Emerging therapies beyond lasers

CHERYL GUTTMAN KRADE, BS PHARM | Staff Correspondent

ACOUSTIC SHOCKWAVES, dermal cooling systems, micro-coring skin removal devices and a “smart” needle that guides dermal filler injections are among the emerging therapies that could change dermatologic surgeons’ treatment options for medical and cosmetic patients over the next few years, according to Mathew M. Avram, MD, JD, who led a session on the future of skincare at the American Society for Dermatologic Surgery (ASDS)

ANTIAGING CONTINUES ON PAGE 50

Psoriasis

Study examines healthcare costs of psoriasis

ILYA PETROU, MD | Staff Correspondent

PATIENTS WITH PSORIASIS initiating treatment with apremilast (Otezla®, Amgen) and/or switching to the medication during their treatment course have lower healthcare costs compared to those who receive biologics, reports a recent study⁴. However, while this oral phosphodiesterase-4 (PDE4) inhibitor can be effective for treating moderate cases of the disease, biologics or combinations of treatments still may be better solutions for patients with severe psoriatic symptoms.

Apremilast is indicated for the treatment of adult patients APREMILAST CONTINUES ON PAGE 39

Emerging therapies beyond lasers

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EMERGING THERAPIES CONTINUES ON PAGE 50

Clinical insights that expand expertise and advance practice

DERMATOLOGY TIMES.com
Every day, dermatologists and their teams, healthcare providers and manufacturers/suppliers working in the field of dermatology redefine what’s possible for patient treatment and care. Whether treating patients in their private practices, conducting seminal studies, exploring new therapies, techniques and technology or teaching the next generation of dermatologic specialists, the medical community involved in this specialty finds ways to push the boundaries of what is into a future of what’s needed to optimize the health and quality of life (QoL) for their patients.

There is no “can’t”; there’s only what if. Solving the ongoing challenges posed by acne, rosacea, atopic dermatitis, psoriasis, skin cancer and aging requires continued innovation. But, that goes far beyond helping to develop new devices or therapies. Dermatologists are leading patient management into new territory, emphasizing QoL, addressing issues surrounding skin of color, and the need for more ethnically diverse studies, and working to make care more affordable and accessible. DermatologyTimes® created its Giants of Dermatology award to recognize and celebrate the visionary physicians at the forefront of change. Their work, dedication and passion make them exemplars of what excellence means in this specialty. As the cover story points out, the lists of “firsts” that make up their bio demonstrate both thought leadership and the sheer perseverance to make the impossible, possible. Alongside their inventions and research are achievements on a human scale: awards for the impossible, possible. Alongside their inventions and thought leadership and the sheer perseverance to make the impossible, possible.

We would also like to thank our distinguished advisory board who verified the peer-to-peer nominations:

- Mark G. Lebwohl, MD
- Daniel Mark Siegel, MD, MS, FAAD, FACMS
- Robert S. Kirsten, MD, PhD, FAAD
- C. William Hanke, MD, MPH, FACP
- Jill S. Waibel, MD

In addition, we would like to thank program sponsor, Almirall. For an in-depth look, see our cover story for this issue, and visit dermatologytimes.com to view videos with insights from this year’s honorees. As their work, and the work done every day by those involved in dermatology clearly shows, this specialty has a great deal to celebrate.

Mike Hennessy, Sr., is Chairman and Founder of DermatologyTimes® Parent Company, MJH Life Sciences.

CELEBRATING EXCELLENCE
An IL-23 inhibitor for adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

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**DURABLE**
Most patients achieved PASI 90 at Week 16 and maintained it at Week 52.

**RAPID**
Co-primary endpoints of PASI 90 and sPGA 0/1 at Week 16, including response 4 weeks after first dose.

**CLEAR**
The majority of patients achieved PASI 100 at Week 52.

**4 DOSES PER YEAR**
Reliable 3-month dosing after 2 initiation doses at Weeks 0 and 4 (150 mg per dose).

Nothing less than the opportunity for durable skin clearance.
For your patients, that’s everything.

**SAFETY CONSIDERATIONS**
SKYRIZI may increase the risk of infection. Instruct patients to report signs or symptoms of clinically important infection during treatment. Should such an infection occur, discontinue SKYRIZI until infection resolves. Evaluate patients for tuberculosis infection prior to initiating treatment with SKYRIZI. Avoid use of live vaccines in SKYRIZI patients.

Please see additional Important Safety Information on the inside spread.
Please see the Brief Summary of the full Prescribing Information on the last page of this ad.

AbbVie
# ACHIEVEMENTS AT WEEK 16 IN ULTIMMA-1 & ULTIMMA-2 (NRI)²

## CO-PRIMARY ENDPOINTS (P<0.0001)

<table>
<thead>
<tr>
<th></th>
<th>PASI 90 at Week 16</th>
<th>sPGA 0/1 at Week 16</th>
<th>PASI 100 at Week 16</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ULTIMMA-1</td>
<td>ULTIMMA-2</td>
<td>ULTIMMA-1</td>
</tr>
<tr>
<td>SKYRIZI</td>
<td>75% (229/304)</td>
<td>75% (220/294)</td>
<td>36% (109/304)</td>
</tr>
<tr>
<td>PLACEBO</td>
<td>5% (5/102)</td>
<td>2% (2/98)</td>
<td>0% (0/102)</td>
</tr>
</tbody>
</table>

NRI: Non-Responder Imputation.

**Study Design:** ULTIMMA-1 (N=506) and ULTIMMA-2 (N=491) were replicate phase 3, randomized, double-blind, placebo- and active-controlled studies to evaluate the efficacy and safety of SKYRIZI (150 mg) vs placebo over 16 weeks and biologic active control over 52 weeks in adult patients with moderate to severe plaque psoriasis. SKYRIZI (150 mg) was given as 2 subcutaneous injections at Weeks 0, 4, and every 12 weeks thereafter.

## CONSISTENT PASI 90/100 RATES AT 2.5 YEARS IN OPEN-LABEL EXTENSION³

Participants received treatment at Week 0, Week 4, and every 12 weeks thereafter.

<table>
<thead>
<tr>
<th></th>
<th>PASI 90</th>
<th>sPGA 0/1</th>
<th>PASI 100</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=408/464)</td>
<td>(n=295/464)</td>
<td>(n=375/408)</td>
</tr>
<tr>
<td>SKYRIZI</td>
<td>88%</td>
<td>84%</td>
<td>88%</td>
</tr>
<tr>
<td>PLACEBO</td>
<td>5%</td>
<td>5%</td>
<td>0%</td>
</tr>
</tbody>
</table>

**Note:** Analysis conducted 8/6/2019.

---

## INTEGRATED RESULTS FROM ULTIMMA-1 AND 2 — ALL DATA ARE AS OBSERVED

- Patients who achieved PASI 90 and PASI 100 (%)
- Study week: 4, 16, 28, 40, 52, 64, 76
- Double-Blind RCT
- Open-Label Extension

**STUDY DESIGN:** The data presented here are drug often drop out. In patients with a chronic infection or a history of recurrent infection, consider the risks and benefits prior to prescribing SKYRIZI. Instruct patients to seek medical advice if signs or symptoms of clinically important infection occur. If a patient develops such an infection or is not responding to standard therapy, closely monitor and discontinue SKYRIZI until the infection resolves.

**Pre-Treatment Evaluation for Tuberculosis (TB)**
- Prior to initiating treatment with SKYRIZI, evaluate for TB infection and consider treatment in patients with latent or active TB for whom an adequate course of therapy cannot be confirmed. Monitor patients for signs and symptoms of active TB during and after treatment.

---

**INDICATION¹**

SKYRIZI® is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.

**IMPORTANT SAFETY INFORMATION¹**

**Infection**
- SKYRIZI® (risankizumab-rzaa) may increase the risk of infection. Do not initiate treatment with SKYRIZI in patients with a clinically important active infection until it resolves or is adequately treated.

---

**EXPLORE LONG-TERM DATA AT VIEWTHEDATA.COM**
SKYRIZI® (risankizumab-rzaa) may increase the risk of infection. Important Safety Information

**INDICATION**

SKYRIZI is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.

**ACHIEVEMENTS AT WEEK 16 IN ULTIMMA-1 & ULTIMMA-2 (NRI)**

- **PASI 90 at Week 16**
  - **SKYRIZI: 88%**
  - **PLACEBO: 5/102**
- **sPGA 0/1 at Week 16**
  - **SKYRIZI: 88%**
  - **PLACEBO: 8%**

**TREATMENT TO WEEK 136**

- **PASI 90 at Week 136**
  - **SKYRIZI: 64%**
  - **PLACEBO: 2%**
- **sPGA 0/1 at Week 136**
  - **SKYRIZI: 84%**
  - **PLACEBO: 8%**

**STUDY DESIGN:** The data presented here are a sub-analysis of LIMMitless (OLE) and include only patients from ultIMMa-1 and 2 who were originally randomized to SKYRIZI, completed the RCT, and enrolled in the OLE. LIMMitless is an open-label extension for which patients who completed either ultIMMa trial, IMMhance, or IMMvent were eligible to participate.

**OLE LIMITATIONS:** In an open-label extension, there is potential for enrichment of the long-term data in the remaining patient populations since patients who are unable to tolerate or do not respond to the drug often drop out.

**STUDY WEEK**

- 88
- 100
- 112
- 124
- 136

Open-Label Extension (Analysis 8/6/2019)

**REFERENCES:**

1. SKYRIZI [package insert]. North Chicago, IL: AbbVie Inc.

**IMMUNIZATIONS**

- Prior to initiating SKYRIZI, consider completion of all age appropriate immunizations according to current immunization guidelines. Avoid use of live vaccines in patients treated with SKYRIZI.

**ADVERSE REACTIONS**

- Most common (≥1%) adverse reactions associated with SKYRIZI include upper respiratory infections, headache, fatigue, injection site reactions, and tinea infections.
Infections
Adverse drug reactions that occurred in < 1% but > 0.1% of subjects in the SKYRIZI group and at a higher rate in the SKYRIZI group than the placebo group during the 16-week controlled period of pooled clinical studies. A total of 1248 subjects were exposed to SKYRIZI for at least one year. Because clinical trials are conducted under widely varying conditions, adverse drug reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Table 1. Adverse Drug Reactions Occurring in 1% or More of Subjects on SKYRIZI through Week 16

<table>
<thead>
<tr>
<th>Adverse Drug Reaction</th>
<th>SKYRIZI (N = 1663)</th>
<th>Placebo (N = 300)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>3.1 (52)</td>
<td>0.7 (2)</td>
</tr>
<tr>
<td>Headache</td>
<td>15.8 (257)</td>
<td>11.0 (33)</td>
</tr>
<tr>
<td>Injection site reactions</td>
<td>14.5 (243)</td>
<td>15.1 (23)</td>
</tr>
<tr>
<td>Sinus headache</td>
<td>2.4 (39)</td>
<td>0.7 (2)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>2.4 (39)</td>
<td>0.7 (2)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>3.7 (61)</td>
<td>0.7 (2)</td>
</tr>
<tr>
<td>Tonsillitis</td>
<td>1.1 (18)</td>
<td>0.7 (2)</td>
</tr>
<tr>
<td>Tinea infections</td>
<td>15.0 (249)</td>
<td>13.3 (40)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>11.3 (187)</td>
<td>3.3 (10)</td>
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</tbody>
</table>

• Includes: headache, tension headache, sinus headache, cervicogenic headache
• Includes: rash, arthralgia, arthralgias, myalgia, myalgias, influenza-like illness, fever, chills, back pain, pharyngitis, infection, nasopharyngitis, sinusitis, rhinitis, pharyngitis, tonsillitis, sinusitis, tinea infections

Adverse drug reactions that occurred in ≥ 1% but < 10% of subjects in the SKYRIZI group and at a higher rate than the placebo group through Week 16 were:

- Fatigue
- Nasopharyngitis
- Pharyngitis
- Tonsillitis

Adverse drug reactions that occurred in ≥ 1% but < 10% of subjects in the placebo group were:

- Fatigue
- Nasopharyngitis
- Pharyngitis
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Adverse drug reactions that occurred in ≥ 1% but < 10% of subjects in the placebo group were:

- Fatigue
- Nasopharyngitis
- Pharyngitis
- Tonsillitis

Prevention of Therapeutic Failure
Evaluate patients for tuberculosis (TB) prior to initiating treatment with SKYRIZI. Assess the clinical setting of the patient, the patient’s risk factors for TB, and the risk of therapeutic failure to determine the need for TB prophylaxis. Instruct patients or caregivers to administer two 75 mg single-dose syringes to achieve the 150 mg dose of SKYRIZI. Instruct patients or caregivers to perform the first self-injected dose under the supervision and guidance of a qualified health care professional for training in proper preparation and administration of SKYRIZI, including cleaning and disposal of the needle and syringe. When a patient is self-administering, they should perform their first self-injected dose under the supervision of a qualified health care professional or have the injection performed by a qualified health care professional.


develop antibodies to risankizumab-rzaa. Of the subjects who developed antibodies to risankizumab-rzaa, 1533 (84.3%) had antibodies prior to baseline and developed antibodies during the study. No antibodies were detected in 1663 (98.5%) of the subjects who were antibody-negative at baseline.

Infections
Infections were reported in 1.9% of patients treated with SKYRIZI (N = 1208). The rate of serious infections for the SKYRIZI group was 0.4% (N = 49). Serious infections in the SKYRIZI group included cellulitis, abscesses, septic events, and sepsis. Evaluation through Week 52, of the rate of infections (2.3% of 1208 subjects treated) was similar to the rate observed during the first 16 weeks of treatment.

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ANTIAGING
Emerging therapies explore skincare solutions beyond lasers
Novel modalities could be on the market as early as 2021.

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AMA Study

Competition shrinks as health insurance markets concentrate

The study also found that payer sway in a region hurts not only patient care, but also physician pay.

BY KEITH A. REYNOLDS

Competition and choice are seemingly going the way of the dodo for many patients as commercial health markets continue to concentrate.

According to the American Medical Association (AMA) analysis Competition in Health Insurance: A Comprehensive Study of U.S. Markets, between 2014 and 2019 the share of markets that were highly concentrated increased from 71% to 74% and 52% of highly concentrated markets in 2014 grew even more concentrated five years later.

These conditions can negatively affect the amount reimbursed for medical services to physicians and other providers.

“When an insurer exercises market power in its input market (eg, physician services), payments to health care providers are below competitive levels,” the introduction to the study says.

It is important to note that when payers have competitive sway over an area it also harms physicians, not just patients, in that the insurer can pay lower reimbursements because physicians don’t have a choice but accept patients on those monopsony-like health plans.

“For many of the 70 million Americans who live in highly concentrated health insurance markets, a lack of competition is a problem that keeps getting worse.”

– AMA President Susan R Bailey, MD

“For many of the 70 million Americans who live in highly concentrated health insurance markets, a lack of competition is a problem that keeps getting worse as consumers have more limited health insurance options to choose,” AMA President Susan R Bailey, MD, says in a news release accompanying the study. “The AMA strongly encourages a dialogue among regulators, policymakers, lawmakers, and others about the need for a better, more open and competitive marketplace to benefit patients and the physicians who care for them.”

The analysis looked at all 384 metropolitan statistical areas (MSAs), the 50 states, and the District of Columbia using the Herfindahl-Hirschman Index (HHI). Those markets which exceed 2500 points are considered highly concentrated, according to federal guidelines.

The release lays out the health insurance market in Elizabethtown-Fort Knox, Kentucky, as an illustration of the increased stranglehold certain payers hold in some areas. This MSA market had an HHI of 3,534 in 2014, which exceeds federal thresholds for a highly concentrated market by more than 1,000 points. That number jumped by 1,625 to an HHI of 5,159.

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DECEMBER 2020 DermatologyTimes®
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- Wireless Foot Pedal
- Preset Protocols
- Portable / Affordable

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- Carry Case
- Two Year Warranty

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~ Dina N. Anderson, MD
Dermatologist, Clinical Instructor
Mount Sinai, New York City

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**A NOVEL ORAL TETRACYCLINE DEVELOPED SPECIFICALLY FOR MODERATE TO SEVERE ACNE IN PATIENTS AS YOUNG AS 9†**

*With spontaneous mutation frequencies being $10^{-10}$ at 4–8 × MIC.*

† **STUDY DESIGN:** The safety and efficacy of SEYSARA was assessed in two identically designed, 12-week, multicenter, randomized, double-blind, placebo-controlled trials. In both studies, SEYSARA was administered orally once daily for 12 weeks as 60-mg, 100-mg, or 150-mg tablets, based on patient weight. **STUDY RESULTS:** Mean absolute reduction (co-primary endpoint) was 15.3 in study 1 (SC1401) and 15.5 in study 2 (SC1402) vs 10.2 and 11.1 in the placebo groups at Week 12, respectively. Overall, 21.9% of ITT patients in study 1 and 22.8% of ITT patients in study 2 achieved IGA success (co-primary endpoint), defined as ≥2-point improvement from baseline in IGA scale for inflammatory lesions of acne and a score of 0 (clear) or 1 (almost clear), at Week 12 vs 10.5% and 15.3% of patients with placebo, respectively ($P < .0001$ for study 1 and $P = .0038$ for study 2).

**INDICATIONS AND USAGE**

SEYSARA (sarecycline) tablet, is indicated for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years of age and older.

**Limitations of Use:** Efficacy of SEYSARA beyond 12 weeks and safety beyond 12 months have not been established. SEYSARA has not been evaluated in the treatment of infections. To reduce the development of drug-resistant bacteria as well as to maintain the effectiveness of other antibacterial drugs, SEYSARA should be used only as indicated.

**IMPORTANT SAFETY INFORMATION**

**CONTRAINDICATIONS**

SEYSARA is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

**WARNINGS AND PRECAUTIONS**

- Like other tetracyclines, SEYSARA can cause fetal harm when administered to a pregnant woman. If SEYSARA is used **during pregnancy,** or if the patient becomes pregnant while taking SEYSARA, the patient should be informed of the potential hazard to the fetus and treatment should be stopped immediately.

- The use of SEYSARA during **tooth development** (second and third trimesters of pregnancy, infancy, and childhood up to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown).

- **Clostridium difficile associated diarrhea (CDAD) has been reported with nearly all antibacterial agents, and may range in severity from mild diarrhea to fatal colitis. If *Clostridium difficile* Associated Diarrhea (antibiotic associated colitis) occurs, discontinue SEYSARA.**

- **Central nervous system side effects,** including light-headedness, dizziness or vertigo, have been reported with tetracycline use. Patients who experience these symptoms should be cautioned about driving vehicles or using hazardous machinery. These symptoms may appear during therapy and may disappear when the drug is discontinued.
SEYSARA:
AN ORAL ANTIBIOTIC THAT’S ON TARGET FOR ACNE

LOW ANTIBIOTIC RESISTANCE IN ACNE

- Propionibacterium acnes strains displayed a low propensity for the development of resistance to sarecycline.1-3
- Sarecycline is active in vitro against most isolates of P. acnes; however, the clinical significance is unknown.1

PROVEN EFFICACY IN FACIAL AND TRUNCAL ACNE

- Significant inflammatory lesion count reduction on the face at Week 12 and as early as Week 3.†
- The only oral antibiotic for acne with significant facial and truncal efficacy data.3

SAFETY AND TOLERABILITY DATA UP TO 12 MONTHS†

- An established safety profile with low rates of GI, vestibular, and phototoxic side effects.1-3
- The most common adverse reaction in pivotal trials was nausea (incidence ≥1%).†

Please see Limitations of Use and Warnings and Precautions regarding bacterial resistance below.

CHOOSE SEYSARA: THE ONE AND ONLY ORAL ANTIBIOTIC DEVELOPED SPECIFICALLY FOR ACNE

- Intracranial hypertension in adults and adolescents has been associated with the use of tetracyclines. Clinical manifestations include headache, blurred vision and papilledema. Although signs and symptoms of intracranial hypertension resolve after discontinuation of treatment, the possibility for sequelae such as visual loss that may be permanent or severe exists. Concomitant use of isotretinoin and SEYSARA should be avoided because isotretinoin, a systemic retinoid, is also known to cause intracranial hypertension.

- Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while using SEYSARA.

- Bacterial resistance to tetracyclines may develop in patients using SEYSARA. Because of the potential for drug-resistant bacteria to develop during the use of SEYSARA, it should only be used as indicated.

- As with other antibiotic preparations, use of SEYSARA may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, SEYSARA should be discontinued and appropriate therapy instituted.

ADVERSE REACTIONS

Most common adverse reaction (incidence ≥1%) is nausea.

Please turn the page for Brief Summary of full Prescribing Information.

GI, gastrointestinal; IGA, investigator’s global assessment; ITT, intent-to-treat; MIC, minimum inhibitory concentration.

References:

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Narrow-spectrum antibiotics viable treatment option for acne

MORGAN PETRONELLI | Assistant Editor

The use of antibiotics for treatment of acne vulgaris has been around for decades. However, in recent years, the perception of antibiotics has changed due to the possibility for development of antibiotic resistance.

Christopher Bunick, MD, PhD, associate professor of dermatology at Yale School of Medicine, spoke with Dermatology Times in a podcast interview about the history of antibiotic use for acne and how new treatment options are pushing the envelope to change the drug’s stigma.

The use of antibiotics as a treatment for acne can be attributed to the drug’s anti-bacterial and anti-inflammatory properties to help with skin clearance, according to Bunick. Tetracycline is the most commonly prescribed class of antibiotics, with some of the most popular oral medications including doxycycline, minocycline and newly approved sarecycline.

“Perceptions about the use of oral antibiotics in acne have changed largely due to public concerns over the development of antibiotic resistance, causing dermatologists to think more about duration of antibiotic therapy and which drug has the least propensity for developing resistance,” says Bunick.

He adds that the concern for patients developing antibiotic resistance can be attributed to a specific group of antibiotics — broad-spectrum antibiotics, defined as an antibiotic that targets a large variety of bacterial species. These types of antibiotics are concerning due to the possibility that they could harm some of the good bacterial species that make up the skin’s microbiome, says Bunick. Some of these broad-spectrum antibiotics include doxycycline, minocycline, tetracycline, azithromycin, amoxicillin, trimethoprim and sulfamethoxazole.

Bunick says when antibiotic resistance occurs, the medication possibly no longer helps treat the patient’s acne, as well as altering the skin and gut microbiome (microbial dysbiosis), and increasing difficulty in treating infections.

However, narrow-spectrum antibiotics target fewer bacterial species, leading to decreased chance of developing antibiotic resistance. Some narrow-spectrum antibiotics include sarecycline, fidaxomicin, vancomycin and bedaquiline, with sarecycline being the only narrow-spectrum antibiotic approved for acne. While effective against C. acnes, Sarecycline has shown reduced in-vitro activity against Gram-negative bacteria commonly found in the human gut.

When prescribing his acne patients antibiotics, Bunick underscores the importance of communication by explaining to patients that with any medication, there is the potential for adverse events.

“One of the most common ways dermatologists currently seek to reduce the potential for drug resistance is to use combination therapy. This could take many forms: for mild to moderate acne, it could mean a combination of topical agents (topical antibiotics combined with benzoyl peroxide and/or retinoids),” he says. “For moderate to severe inflammatory acne, and for patients with truncal acne who want faster results, oral antibiotics may be ideal first line and can be combined with topical agents too. However, I would try to use narrow-spectrum oral antibiotics when feasible to reduce unwanted side effects.”

Recently, Bunick worked alongside Yury Polikanov, PhD, associate professor of biological sciences at University of Illinois at Chicago, to investigate how the C-7 moiety of narrow-spectrum antibiotic sarecycline influences its ability to bind to the 30S subunit of the 70S ribosome versus other tetracycline class antibiotics and interpret its mechanism of action.

The study’s findings were published in the Proceedings of the National Academy of Sciences, and the crystal structure of sarecycline bound to the 70S ribosome showed, similar to other antibiotics, that sarecycline binds at the “decoding center” of the small 30S ribosomal subunit.

Also, the results found sarecycline’s C7 moiety leads into the messenger RNA channel, with the potential of interference with mRNA movement through the channel and disruption of codon-anticodon interactions that the ribosome needs in order to translate mRNA into protein.

“This mechanism of action of direct mRNA contact by sarecycline had not been previously observed by any tetracycline antibiotic and is directly a consequence of the chemical moiety unique to sarcycline’s C7 position,” adds Bunick.

The study’s findings demonstrate that sarecycline has a unique mechanism of action that could explain its low propensity for development of antimicrobial resistance and narrow-spectrum activity.

“This work emphasizes an important point – that the various tetracycline acne medications cannot simply be lumped into one category and presumed to work the same. Our data shows that the different chemical modifications on doxycycline, minocycline and now sarecycline, make a difference in the mechanism of action,” says Bunick.
People assume employees don't sue happy offices. That's not correct.

Age discrimination in the era of COVID

by DAVID J. GOLDBERG, M.D., J.D.

Dr. Goldberg is director of Skin Laser and Surgery Specialists of New York and New Jersey, past director of Mohs and Laser Research, Icahn School of Medicine at Mt. Sinai; and, adjunct professor of law, Fordham Law School in New York City.

Doctor Doc has a large practice with many productive, happy employees. Unfortunately, the pandemic has forced him to terminate many employees. One of these employees, an elderly woman who had worked with him for more than 20 years, had become increasingly combative. He wanted to terminate her for years but was afraid she would file an age discrimination lawsuit.

He tells other staff members that the pandemic finally gave him the opportunity to “get rid of her.” He terminates her on the spot. Immediately his office becomes calmer and more productive. Six months later he receives notification that he is the defendant in an age discrimination lawsuit by the former employee. How can this be?

The general assumption is that employees do not sue happy, worker-friendly companies like most dermatology offices. Employee lawsuits supposedly happen in companies with bad bosses, poor working conditions and hostile environments. This is just not correct.


Dermatologists do need protection, and that starts with bulletproofing human resources (HR) documentation:

1. **MAKE THE EMPLOYEE HANDBOOK REQUIRED READING**
   Spell out company HR policies in writing. Use a consultant experienced in employment law to help create or review the manual. Require managers and employees to sign off on their receipt and acceptance of baseline employment policies when they start.

2. **FOLLOW THE LAW**
   Post government-required documents. Make sure you know what is required, and do it. Create and maintain a good filing system with a secure place for sensitive information. Store employee personnel, medical and confidential records separately to prevent unauthorized staff from accessing privileged information. There is no need to create a medical or confidential file for each employee. But, should the occasion arise, that information should not be placed into the main personnel file.

3. **IMPLEMENT A DOCUMENT RETENTION POLICY**
   What HR documents do you need to keep? What files, paper or digital, can or should be discarded on a regular basis? Old emails and other digital records can help or hurt the company. Deleting them on a schedule might be a good idea. But there must be a written policy—and the company must stick to it.

4. **CONDUCT PERFORMANCE REVIEWS**
   The performance review is your main opportunity to document an employee’s failure to meet expectations. Be specific. You can—and must—inform an employee on what he or she is doing wrong, and warn of the consequences if performance or behavior does not improve. Take notes to document the meeting and include an account of the employee’s responses. Work together to formulate an action plan for improvement, with a clear time frame. Put it in writing. Have both parties sign it. Revisit it together at the planned dates.

5. **TERMINATE COMPASSIONATELY**
   If reviews are done properly, no termination should come as a surprise. But, it is always unpleasant for the person being terminated. Maintain a calm and compassionate attitude and steer the employee toward finding new employment that is a better fit, rather than seeking retribution through legal action.

Termination of the employee by Doctor Doc could and should have been easy process. Had he taken the above approach a lawsuit likely would not have happened.
What is PRP?
PRP stands for platelet rich plasma. The normal platelet count in human blood is 150,000-350,000/microliter. PRP is defined as one million platelets per microliter in a small volume of plasma with a full complement of clotting factors. There are seven key growth factors in PRP: platelet-derived growth factors (PDGFaa, PDGFbb, PDGFab), transforming growth factors (TGF-b1, TGFb2), vascular endothelial growth factor (VEGF), and epithelial growth factor (EGF). Cellular mitogenesis and angiogenesis are both upregulated by PRP, making it useful in facial rejuvenation.

How is PRP obtained and prepared?
PRP is obtained from freshly drawn blood with an added anticoagulant. The blood is centrifuged twice. The first spin, known as the hard spin, separates the red blood cells from the plasma containing the platelets, white blood cells, and clotting factors. Three layers result from the hard spin: an upper layer containing platelets and white blood cells, a middle layer known as the buffy coat containing white blood cells, and a bottom layer containing red blood cells. The red blood cell layer is removed and discarded.

The second spin, known as the soft spin, separates the platelet-rich plasma in the bottom of the tube from the platelet-poor plasma (PPP) in the top of the tube by removing more red blood cells.

How does PRP work?
PRP works through degranulation of the alpha granules in platelets, which contain the growth factors. It is ideal to collect PRP in an anticoagulated state for the growth factors to remain active, which explains the need to draw the blood into a tube containing sodium citrate. The biologically active cellular components such as the growth factors are preserved within the platelet when the platelet is held in an inactive state.

Upon activation of the platelet, the granules then fuse to the cell membrane, activating the secretory growth factors, which bind to the transmembrane receptors of target cells, such as mesenchymal stem cells, fibroblasts, endothelial cells, and epidermal cells. This binding activates intracellular signal proteins that express a gene sequence directing cellular proliferation, collagen synthesis, extracellular matrix formation, and numerous other pathways to promote healing and repair processes.

There are many conflicting reports in the literature about the efficacy of PRP. If the PRP is not properly prepared, there will be no biologic effect. This could be due to improper centrifuge use with a standard laboratory centrifuge rather than specialized U.S. Food and Drug Administration (FDA)-cleared equipment with validated processes.

How is PRP impacting dermatology?
In dermatology, PRP is used via direct injection into the face as the “vampire facial” popular with celebrities. However, topical PRP is the next horizon. However, it must be put into a suitable vehicle that must be refrigerated for twice-daily facial application as a treatment product. Refrigerated (4 degrees C) topical PRP preparations have been shown to be stable for 90 days. At that time the patient must come back to the office for another phlebotomy and PRP preparation session. The vehicle must be specially formulated at the correct pH and with specially selected preservatives that will not destroy the PRP. Doctors should caution patients that PRP topical should be used only by the patient for whom it was prepared, not for other family members or friends since it is a blood-containing product.

PRP is safe in dermatology because it is autologous, thus concerns about immune rejection are a nonissue. PRP contains the same materials present in the bloodstream that induce clotting, except in higher concentration. The growth factors function by activating a cytoplasmic signal that promotes normal gene expression. Because of that, topical PRP represents the first biologically active personalized skin care product.
Spironolactone effective for female teens with acne

Treatment benefits nearly 74% of study subgroup with grade 4 acne.

Quick TAKES

Eighty percent of females aged <21 years treated for refractory acne benefit from spironolactone.

Spironolactone was associated with good safety and tolerability in this pediatric population.

Physicians should prescribe an oral contraceptive but refrain from prescribing antibiotics.

Spironolactone is a safe and effective treatment for female adolescent patients with acne whose disease has not responded to topical therapies, according to the findings of a recently published retrospective study.²

Recognizing the lack of data on the use of spironolactone as treatment for acne in the pediatric population, researchers from the Mayo Clinic, Rochester, Minnesota, undertook an electronic search of their institution’s medical records to identify females aged <21 years who received spironolactone as an acne treatment for at least 3 months. Their analysis included patients aged 14 to 20 years old (median, 19) with a median European classification system acne severity grade of 3 (severe papulopustular/moderate nodular acne). A majority of the patients were unresponsive to previous oral treatments for acne (94%) and received spironolactone as monotherapy (69%).

Spironolactone treatment was associated with good safety and tolerability in this pediatric population.
MINOCYCLINE IS AT YOUR PATIENT’S FINGERTIPS.

Visit AmzeeqHCP.com to learn more.

INDICATIONS AND USAGE
AMZEEQ® (minocycline) topical foam, 4% is indicated for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in adults and pediatric patients 9 years of age and older.

Limitations of Use: This formulation of minocycline has not been evaluated in the treatment of infections. To reduce the development of drug-resistant bacteria as well as to maintain the effectiveness of other antibacterial drugs, AMZEEQ should be used only as indicated.

IMPORTANT SAFETY INFORMATION
Contraindications: Persons who have shown hypersensitivity to any of the tetracyclines or any other ingredient in AMZEEQ.

Warnings and Precautions
Flammability: The propellant in AMZEEQ is flammable. Instruct the patient to avoid fire, flame, and smoking during and immediately following application.

AMZEEQ is a topical foam. While systemic absorption of AMZEEQ is low, and serious adverse reactions were not seen in clinical studies, the following adverse reactions associated with oral minocycline should be considered:

IMPORTANT SAFETY INFORMATION (cont.)

- Teratogenic effects, inhibition of bone growth & permanent tooth discoloration: Use during the second and third trimesters of pregnancy, infancy and childhood up to the age of 8 years may cause permanent discoloration of the teeth (yellow-gray-brown) and reversible inhibition of bone growth.
- Clostridium difficile associated diarrhea (CDAD): If CDAD occurs, discontinue AMZEEQ.
- Hepatotoxicity & metabolic effects: If renal impairment exists or if liver injury suspected, discontinue AMZEEQ.
- Central nervous system effects: Patients experiencing light-headedness, dizziness or vertigo should be cautioned about driving vehicles or operating heavy machinery.
- Intracranial hypertension: Clinical manifestations include headache, blurred vision, diplopia, and vision loss. Discontinue AMZEEQ immediately if symptoms occur.
- Autoimmune syndromes: Symptoms may be manifested by fever, rash, arthralgia, and malaise. Discontinue AMZEEQ immediately if symptoms occur.

REFERENCES: 1

1. Amzeeq ® (minocycline) topical foam, 4% Prescribing Information.


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THE FIRST AND ONLY TOPICAL MINOCYCLINE FOR ACNE
FOR YOUR PATIENTS WITH INFLAMMATORY LESIONS OF MODERATE TO SEVERE ACNE VULGARIS.

The minocycline you know and trust.¹
• In large, 12-week trials, Amzeeq demonstrated an improvement vs. vehicle foam in both inflammatory lesions and IGA scores.¹ ²
• The most commonly reported adverse reaction was headache (3%).¹ ²

The tolerability of a gentle foam.¹
• Proprietary oil-based foam vehicle contains natural moisturizing ingredients without drying agents like ethyl alcohol.¹ ³ ⁴

The innovation you’ve been waiting for.
• Molecule Stabilizing Technology (MST)™ enables minocycline to be placed into a lipophilic vehicle for stable topical delivery.¹ ² ³

IMPORTANT SAFETY INFORMATION (cont.)
• Photosensitivity: Patients should minimize or avoid exposure to natural or artificial sunlight while using AMZEEQ. Advise patients to discontinue treatment with AMZEEQ at the first evidence of sunburn.
• Hypersensitivity reactions: Discontinue AMZEEQ immediately if symptoms of anaphylaxis, serious skin reactions, erythema multiforme, and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome occur.
• Tissue hyperpigmentation: Discoloration of organs, including nails, bone, skin, eyes, thyroid, visceral tissue, oral cavity (teeth, mucosa, alveolar bone), sclerae and heart valves.
• Superinfection: Overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, discontinue AMZEEQ and institute appropriate therapy.

Adverse Reactions: The most common adverse reaction reported during clinical trials of AMZEEQ was headache.

* Caprimary endpoints at Week 12 were: Absolute change from baseline in inflammatory lesion count and IGA endpoint success. IGA success was defined as an IGA score of 0 or 1 (clear or almost clear), and at least a 2-grade improvement (decrease). IGA = Investigator’s Global Assessment. 2418 patients were included if they had 20-50 inflammatory lesions (papules, pustules, nodules) and 25-100 noninfl ammatory lesions (open, closed comedones) and an IGA score on a 6-point scale of moderate or severe (grade 3 or 4).
† Amzeeq 4% topical foam contains the following inactive ingredients: soybean oil, coconut oil, light mineral oil, cyclomethicone, cetostearyl alcohol, stearic acid, myristyl alcohol, hydrogenated caster oil, white wax (beeswax), stearyl alcohol, dioctanol, and propellants (butane + isobutane + propane).


See Brief Summary of Prescribing Information for AMZEEQ on following pages.

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AMZEQ® (minocycline) topical foam, 4%  
BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION. PLEASE SEE FULL PRESCRIBING INFORMATION.

INDICATION
AMZEQ is indicated for the topical treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in adults and pediatric patients 9 years of age and older.

Limitations of Use: This formulation of minocycline has not been evaluated in the treatment of infections. To reduce the development of drug-resistant bacteria as well as to maintain the effectiveness of other antibacterial drugs, AMZEQ should be used only as indicated.

CONTRAINDICATIONS
This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines or any other ingredients within AMZEQ.

WARNINGS AND PRECAUTIONS
- Flammability: The propellant in AMZEQ is flammable. Instruct the patient to avoid fire, flame, and smoking during and immediately following application. Do not puncture and/or incinerate the containers. Do not expose containers to heat and/or store at temperatures above 120°F (49°C).
- Teratogenic Effects: Minocycline, like other tetracycline-class drugs, may inhibit bone growth when administered orally during pregnancy. Based on animal data, when administered orally, tetracyclines cross the placenta, are found in fetal tissues, and can cause skeletal malformation and retardation of skeletal development on the developing fetus.
- Tooth Discoloration: The use of tetracycline class drugs orally during tooth development causes discoloration in the permanent teeth. Use of tetracycline drugs is not recommended during tooth development. The safety and effectiveness of AMZEQ have not been established in pediatric patients less than 9 years of age.
- Inhibition of Bone Growth: All tetracyclines form a stable calcium complex in any bone-forming tissue. A decrease in fibula growth rate has been observed in premature human infants given oral tetracycline in doses of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the drug was discontinued. The safety and effectiveness of AMZEQ have not been established in patients less than 9 years of age. Results of animal studies indicate that oral tetracyclines cross the placenta, are found in fetal tissues, and can cause retardation of skeletal development on the developing fetus. Evidence of embryotoxicity has been noted in animals treated orally early in pregnancy.
- Clostridium difficile Associated Diarrhea: Clostridium difficile associated diarrhea (CDAD) has been reported with nearly all antibacterial agents, including oral minocycline, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile. C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterials. If CDAD is suspected or confirmed, antibiotic use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.
- Hepatotoxicity: Post-marketing cases of severe liver injury, including irreversible drug-induced hepatitis and fulminant hepatic failure (sometimes fatal) have been reported with oral minocycline use in the treatment of acne.
- Metabolic Effects: The anti-anabolic action of the tetracyclines may cause an increase in blood urea nitrogen (BUN). In patients with significantly impaired function, high serum levels of tetracycline-class drugs may lead to azotemia, hyperphosphatemia, and acidosis. If renal impairment exists, recommended oral or parenteral doses may lead to excessive systemic accumulations of the drug and possible liver toxicity. Under such conditions, adjust the dose downward, and if therapy is prolonged, serum level determinations of the drug may be advisable.
- Central Nervous System Effects: Central nervous system side effects including light-headedness, dizziness or vertigo have been reported with oral minocycline therapy. Patients who experience these symptoms should be cautioned about driving vehicles or using hazardous machinery while on minocycline therapy. These symptoms may disappear during therapy and may disappear when the drug is discontinued.
- Intracranial Hypertension: Intracranial hypertension has been associated with the use of tetracycline-class drugs. Clinical manifestations of intracranial hypertension include headache, blurred vision, diplopia and vision loss; papilledema can be found on fundoscopy. Women of childbearing age who are overweight or have a history of I or II are at a greater risk for developing intracranial hypertension. Patients should be questioned for visual disturbances prior to initiation of treatment with tetracyclines. Concurrent use of isotretinoin and tetracycline should be avoided because isotretinoin, a systemic retinoid, is also known to cause intracranial hypertension. Although intracranial hypertension typically resolves after discontinuation of treatment, the possibility for permanent visual loss exists. If visual disturbance occurs during treatment, postmarketing ophthalmologic evaluation is so advised. If use of intracranial pressure can remain elevated for weeks after drug cessation, patients should be monitored until they stabilize.
- Autoimmune Syndromes: Tetracyclines have been associated with the development of autoimmune syndromes. Long-term use of oral minocycline in the treatment of acne has been associated with drug-induced lupus-like syndrome, autoimmune hepatitis and vasculitis. Sporadic cases of serum sickness have been reported shortly after oral minocycline use. Symptoms may be manifested by fever, rash, arthralgia, and malaise. In symptomatic patients, immediately discontinue the use of all tetracycline-class drugs, including AMZEQ.
- Photosensitivity: Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking oral tetracyclines; this reaction has been reported less frequently with minocycline. Although AMZEQ did not induce photosensitivity, phototoxicity or photophagia symptoms in human dermatology studies, patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVAB treatment) while using minocycline. If patients need to be outdoors while using AMZEQ, they should wear loose-fitting clothes that protect skin from sun exposure and discuss other sun protection measures with their physician. Advise patients to discontinue treatment with AMZEQ at the first evidence of sunburn.
- Serious Skin/Hypersensitivity Reaction: Cases of anaphylaxis, serious skin reactions (e.g. Stevens Johnson syndrome), erythema multiforme, and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome have been reported postmarketing. DRESS syndrome consists of cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, and one or more of the following visceral complications such as hepatitis, pneumonitis, nephritis, myocarditis, and pericarditis. Fever and lymphadenopathy may be present. In some cases, death has been reported with oral minocycline use. If this syndrome is recognized, discontinue AMZEQ immediately.
- Tissue Hyperpigmentation: Oral tetracyclines are known to cause hyperpigmentation. Tetracycline therapy may induce hyperpigmentation in many organs, including nails, bone, skin, eyes, thyroid, visceral tissue, oral cavity (teeth, mucosa, alveolar bone), sclerae and heart valves. Skin and oral pigmentation has been reported to occur independently of time or amount of drug administration, whereas other tissue pigmentation has been reported to occur upon prolonged administration. Skin pigmentation includes diffuse pigmentation as well as pigmentation over sites of scars or injury.
- Development of Drug-Resistant Bacteria: AMZEQ has not been evaluated in the treatment of infections. Bacterial resistance to the tetracyclines may develop in patients using AMZEQ, therefore, the susceptibility of bacteria associated with infection should be considered in selecting antimicrobial therapy. Because of the potential for drug-resistant bacteria to develop during the use of AMZEQ, it should be used only as indicated.
- Superinfection/Potential for Microbial Overgrowth: Use of AMZEQ may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, discontinue AMZEQ and institute appropriate therapy.

ADVERSE REACTIONS
- Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In a randomized, double-blind, vehicle-controlled trials, subjects age 9 years and older applied AMZEQ or vehicle once daily for 12 weeks. A total of 1,356 subjects were treated with AMZEQ and 1,058 with vehicle. The majority of subjects were White (74%) and female (60%). Approximately 34% were Hispanic/Latino and 49% were younger than 18 years of age.
- The most common adverse reaction reported by ≥1% of subjects treated with AMZEQ and more frequently than in subjects treated with vehicle was

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headache, which was reported in 3% of subjects treated with AMZEEQ and 2% of subjects treated with vehicle. Local tolerability evaluations were conducted at each study visit in the clinical trial by assessment of erythema, dryness, hyperpigmentation, skin peeling and itching. The active assessment of the signs and symptoms of local facial tolerability at Week 12 in subjects treated with AMZEEQ were as follows (mild, moderate, severe): erythema (14.2%, 1.5%, 0%), dryness (6.8%, 0.6%, 0%), hyperpigmentation (12.4%, 2.8%, 0.1%), skin peeling (3.2%, 0.2%, 0%), and itching (3.5%, 0.8%, 0.1%). Hyperpigmentation was most frequently assessed as characteristic of inflammatory and post-inflammatory changes associated with acne. Local tolerability signs and symptoms occurred in similar frequency and severity as subjects treated with the vehicle component of AMZEEQ. In a 40-week open-label extension study (for a total of up to 52 weeks of treatment), frequency and severity of local tolerability signs and symptoms at Week 52 were comparable to those reported at Week 12.

**DRUG INTERACTIONS**

- **Anticoagulants**: Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

- **Penicillin**: Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracycline-class drugs in conjunction with penicillin.

- **Drug/Laboratory Test Interactions**: False elevations of urinary catecholamine levels may occur due to interference with the fluorescence test.

**USE IN SPECIFIC POPULATIONS**

- **Pregnancy**: **Risk Summary**: Available data with AMZEEQ use in pregnant women are insufficient to evaluate a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. Systemic absorption of AMZEEQ in humans is low following once daily topical administration of AMZEEQ for 21 days. Because of low systemic exposure, it is not expected that maternal use of AMZEEQ will result in significant fetal exposure to the drug. Tetracycline-class drugs may cause permanent discoloration of teeth and reversible inhibition of bone growth when administered orally during pregnancy. Animal reproduction studies were not conducted with AMZEEQ. In animal reproduction studies, oral administration of minocycline administered to pregnant rats and rabbits during the period of organogenesis induced skeletal malformations in fetuses at systemic exposures of 750 and 500 times, respectively, the maximum recommended human dose (MRHD; based on AUC comparison) of AMZEEQ (see Data). The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

- **Data/Animal Data**: Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can cause retardation of skeletal development of the developing fetuses. Minocycline induced skeletal malformations (bent limb bones) in fetuses when orally administered to pregnant rats and rabbits during the period of organogenesis at doses of 30 mg/kg/day and 100 mg/kg/day, respectively, (750 and 500 times, respectively, the systemic exposure at the MRHD based on AUC comparison). Reduced mean fetal body weight was observed when minocycline was orally administered to pregnant rats during the period of organogenesis at a dose of 10 mg/kg/day (250 times the systemic exposure at the MRHD based on AUC comparison).

- **Minocycline** was assessed for effects on peri- and post-natal development of rats in a study that involved oral administration to pregnant rats during the period of organogenesis through lactation, at doses of 5, 10, or 50 mg/kg/day. In this study, body weight gain was significantly reduced in pregnant females that received 50 mg/kg/day (650 times the systemic exposure at the MRHD based on AUC comparison). No effects of treatment on the duration of the gestation period or the number of live pups born per litter were observed. Gross external anomalies observed in F1 pups (offspring of animals that received oral minocycline) included reduced body size, improperly rotated feet, and reduced size of extremities. No effects were observed on the physical development, behavior, learning ability, or reproduction of F1 pups, and there was no effect on gross appearance of F2 pups (offspring of F1 animals).

- **Lactation**: **Risk Summary**: Tetracycline-class drugs, including minocycline, are present in breast milk following oral administration. It is not known whether minocycline is present in human milk after topical administration to the nursing mother. There are no data on the effects of minocycline on milk production. Because of the potential for serious adverse reactions, advise patients that breastfeeding is not recommended during treatment with AMZEEQ.

- **Pediatric Use**: The safety and effectiveness of AMZEEQ have been established in pediatric patients 9 years of age and older for the treatment of inflammatory lesions of non-nodulocystic acne vulgaris. AMZEEQ for this indication is supported by three adequate and well controlled 12-week trials in patients 9 years of age and older; two of the trials included a 40-week open-label extension. Additional data was obtained from a 7-day open-label safety and pharmacokinetics study conducted in 20 patients 10 years to less than 17 years of age with acne vulgaris. A total of 686 subjects 9 years of age and older received AMZEEQ in these clinical trials. Safety and effectiveness for this indication have not been established in pediatric patients less than 9 years of age. The use of oral tetracycline drugs during tooth development below the age of 8 years may cause permanent discoloration of the teeth (yellow-gray-brown) and inhibition of bone growth.

- **Geriatric Use**: Clinical studies of AMZEEQ did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

**NONCLINICAL TOXICOLOGY**

- **Carcinogenesis, Mutagenesis, Impairment of Fertility**: In a carcinogenicity study in which minocycline hydrochloride was orally administered to male and female rats once daily for up to 104 weeks at dosages up to 200 mg/kg/day, minocycline hydrochloride was associated in both sexes with follicular cell tumors of the thyroid gland, including increased incidences of adenomas, carcinomas and the combined incidence of adenomas and carcinomas in males, and adenomas and the combined incidence of adenomas and carcinomas in females. In a 2-year study in which minocycline hydrochloride was orally administered to male and female mice once daily for up to 104 weeks at dosages up to 150 mg/kg/day, exposure to minocycline hydrochloride did not result in a significantly increased incidence of neoplasms in either males or females. Minocycline was not mutagenic in vitro in a bacterial reverse mutation (Ames test) or CHO/HTGPRT mammalian cell assay in the presence or absence of metabolic activation. Minocycline was not clastogenic in vitro using human peripheral blood lymphocytes or in vivo in a mouse micronucleus test.

- **Male and female reproductive performance in rats was unaffected by oral doses of minocycline of up to 300 mg/kg/day (10,000 times the systemic exposure at the MRHD based on AUC comparison). However, oral administration of 100 or 300 mg/kg/day of minocycline to male rats (3,800 or 10,000 times, respectively, the systemic exposure at the MRHD based on AUC comparison), adversely affected spermatogenesis. Effects observed at 300 mg/kg/day of oral minocycline included a reduced number of sperm cells per gram of epididymis, an apparent reduction in the percentage of sperm that were motile, and (at 100 and 300 mg/kg/day) increased numbers of morphologically abnormal sperm cells. Morphological abnormalities observed in sperm samples included absent heads, misshapen heads, and abnormal flagella.

- **HANDLING**: Allow the can to warm to room temperature before first use. Shake can well before use.

- **WARNING**: Flammable. Avoid fire, flame, or smoking during and immediately following application. Contents under pressure. Do not puncture or incinerate. Do not expose to heat or temperatures above 49°C (120°F).

For more information, including the FDA-approved Prescribing Information, go to www.amzeq.com or call 1-844-375-3673.

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Adolescent acne therapies benefit younger children

CHERYL GUTTMAN KRADER, BS PHARM | Staff Correspondent

Younger children with acne should be treated the same as adolescents, using combination therapy that may include topical retinoids, benzoyl peroxide and other nonantibiotic agents in combination with antibiotics, according to a recent paper.¹

Written by an expert panel of nine pediatric dermatologists, the article is thought to be the first-ever published report to focus on acne in young pediatric patients and provides a guide to the evaluation and management of acne in children ages birth to 12 years; according to panel member Bernard A. Cohen, MD, Professor of Dermatology and Pediatrics, Johns Hopkins University School of Medicine, Baltimore.

“Acne affects children of all ages,” says Cohen. “With a decline in the age accepted as normal for onset of puberty, we are now seeing acne more often in children who would be categorized as preadolescents based on chronological age. In addition, a number of new medications approved for use in children ages 9 years and older have become available.”

The consensus addresses patient assessment and treatment in an age-related context, including approved and off-label use of the expanded treatment armamentarium. “As a panel participant, it was remarkable to me that our group reached unanimous consensus on all seven statements included in the paper,” he adds.

CONSENSUS CONTENT
Their recently published article presents seven panel-defined consensus statements based on information from 32 articles identified through a systematic literature review together with insights from expert opinion and experience.

Statement 1 in the consensus report categorizes pediatric acne by age, dividing it into the following 5 subgroups: neonatal (birth to ≤8 weeks), infantile (8 weeks to ≤1 year), mid-childhood (1 year to ≤7 years), preadolescent (7 to 12 years), and adolescent (≥12 to 19 years). Investigators summarized presenting features, treatment approaches and red flags that should prompt a further evaluation or referral to a pediatric endocrinologist as they pertain to the neonatal through preadolescent age groups.

Statement 2 highlights the potential psychological impact and permanent physical sequelae of acne in preadolescent age children and underscores the importance of early treatment to minimize emotional distress and facial scarring. “This explains our use of safe and effective therapy at times when the medications are off-label based on age,” says Cohen.

Statement 3 addresses the multifactorial nature of acne pathophysiology. Panel members suggest that hormonal changes are more important than inflammation in preadolescent acne.

Statement 4 reiterates the potential need to conduct a work-up for underlying local and/or systemic pathology in patients with acne, taking into account the individual’s age, skin signs, and general findings from history and physical examination. “Markers of underlying systemic disease associated with markers of precocious puberty, including acne, certainly warrant a medical evaluation and often involvement of our colleagues in pediatric endocrinology,” says Cohen.

Statement 5 looks at unique considerations for treatment of acne in the pediatric population. It notes that well-tolerated and easy-to-use products may be particularly important in ensuring safety and optimizing adherence among children. Also discussed are treatment regimens based on acne severity. A table lists U.S. Food and Drug Administration (FDA)-approved age indications of each product.

Statement 6 looks at problem of resistance. According to the principles of antibiotic stewardship, the consensus was that acne treatment may include use of narrow-spectrum antibiotics, avoiding antibiotic monotherapy and limiting the duration of antibiotic therapy.

Statement 7 of the consensus report reads: “There is still a considerable need for pediatric acne education for pediatric health care providers and their patients.” The panel reinforces the importance of considering whether acne is a sign of endocrine-associated abnormality, recommends off-label use of topical therapies as appropriate in infants and underscores the importance of counseling patients and parents about treatments and their outcomes.

Disclosures: Research for the consensus report was supported by an unrestricted educational grant from Almirall. Dr. Cohen has no relevant financial interests to disclose.

Reference:
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Study links vitamin D deficiency with acne

MARY SCOVIAK | Managing Editor

Vitamin D deficiencies are more frequent in people with acne than in healthy controls, report Ghadah Alhetheli and her coauthors in a first-ever study on this topic in the Kingdom of Saudi Arabia. “This difference is statistically significant with P-value = 0.003,” adds Alhetheli, MD, assistant professor, Department of Dermatology and Cutaneous Surgery, College of Medicine, Qassim University, Buraidah, Saudi Arabia. However, researchers found no significant difference between lower serum 25-hydroxyvitamin D (25 OH) levels and the severity of acne, nor were there substantive variations based on age, gender and sun exposure.

“The precise purpose of vitamin D has yet to be established,” writes Alhetheli and her colleagues. However, because of vitamin D’s regulatory effect on the immune system as well as its antioxidant and anti-comedogenic properties, deficiencies could contribute to the pathogenesis of acne. Alhetheli’s cross-sectional study evaluates serum levels of vitamin D through a representative sample and investigates any correlation with acne severity.

They conducted their study in outpatient dermatology clinics at Qassim University, Saudi Arabia between October 2016 and March 2017 to minimize the effect of seasonal variations on serum vitamin D levels. They enrolled 68 patients with acne vulgaris (27 male, 41 female) and 50 matched healthy controls (24 male, 26 female). Subjects in the patient and control groups had not taken any vitamin D supplement and were not suffering from any comorbidity or complication of vitamin D deficiency. Acne grading was classified as mild in 21 patients (30.88%), moderate in 24 (38.24%), and severe in 21 (30.88%). Inclusion criteria required that male and female patients had been diagnosed with acne vulgaris according to the global acne grading system (GAGS) score. Baseline demographics show that patients with acne were younger than healthy controls, with a mean standard deviation (SD) for males with acne in the study of 20.7 ± 3.8 and 21.3 ± 3.6 for females with acne versus 39.8 ± 11.8 for males in the control group and 39.8 ± 14.85 for females.

Blood samples were collected from patients’ veins and analyzed within 24 hours of sampling using the Roche Cobas e411 (Roche Diagnostic Systems, Rotkreuz, Switzerland). Serum 25-hydroxyvitamin D3 [25 (OH) D] in patients and controls were categorized into adequate (>20 ng/mL), inadequate (12–20 ng/mL), or deficient (<12 ng/mL), following the guidelines of the Food and Nutrition Board of Medicine.

“Our results indicate that serum concentrations of vitamin D in controls were significantly higher than those in acne vulgaris patients (P-value = 0.003),” writes Alhetheli. “These results are in line with several other studies that found no elevation of serum vitamin D levels in acne patients.”

They add that the study data show no relationship between sun exposure and improvement in vitamin D readings in patients with acne.

“This can be explained by several factors, such as the impact of psychological distress on patients with acne’s avoidance of spending extended periods outdoors. This suggests a possible explanation of low vitamin D levels in patients with acne vulgaris,” writes Alhetheli. “These results were consistent with Lim et al who revealed that lower levels of serum vitamin D in severe acne vulgaris patients might be due to psychological stress.”

“We found no significant association between vitamin D deficiency and gender (P-value = 0.199),” says Alhetheli. “The results of our study indicate the mean value of vitamin D was abetted higher in moderate acne (31.44±9) than in mild and severe acne. (26±5.4 and 28.4±6.7, respectively). This difference was not statistically significant (P-value = 0.067), perhaps due to the small sample size of our study. Also, we found no significant relationship between vitamin D deficiency and the severity of acne vulgaris.”

She adds, “This study reveals a statistically significantly low serum vitamin D levels in patients with acne vulgaris. This highlights the importance of screening patients with acne for vitamin D insufficiency and deficiency. Further clinical trials are needed to determine if vitamin treatment with both topical vitamin D analogs and vitamin D supplementation is of significant effect.”

Disclosures: The authors report no conflicts of interest in this work.

References:
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Considering those results along with the results of the present study, we recommend a trial of spironolactone to treat any female aged 14 years or older who has grade 2 to 4 acne that has not responded to topical therapy.”

Somaira Nowsheen, MD, PhD, a dermatology resident currently completing her transitional year at Gundersen Medical Foundation, La Crosse, Wisconsin.

limited side effects during usage periods ranging from 3-to-45 months (median 7 months) and had a benefit in 64 (80%) patients, including in 73.9% of the subgroup of patients with grade 4 (severe nodular/conglobate) acne. In the overall population, the acne responses were rated as complete (290%) in 18 (22.5%) patients, >50% in 29 patients (36.3%), and <50% in 17 patients (21.3%).

RECOMMENDED DOSAGE

“In a previous study we found that females over the age of 21 responded well to spironolactone therapy,” says Somaira Nowsheen, MD, PhD, a dermatology resident currently completing her transitional year at Gundersen Medical Foundation, La Crosse, Wisconsin. “Considering those results along with the results of the present study, we recommend a trial of spironolactone to treat any female aged 14 years or older who has grade 2 to 4 acne that has not responded to topical therapy.” However, she adds that spironolactone should not be used in pregnant women.

Adolescent patients in the study received a daily dose of spironolactone that ranged from 25 to 200 mg with a median of 100 mg. Time to initial response occurred at a median of 5 months. Maximal responses were observed at a median of five months.

“Based on these data, we recommend that spironolactone be used at a dose of 100 mg and for a trial of least 3 months,” Nowsheen says.

OPTIMIZING TREATMENT REGIMENS

The investigators also compared various characteristics of the patients who responded to spironolactone with those of the non-responders to see if they could identify factors associated with a better outcome. Although they did not perform statistical analyses, the numerical data showed that compared with the non-responders, higher percentages of patients whose acne improved had involvement on the jawline (70.3% vs. 56.3%), cyclic flares (75.0% vs. 56.3%), and were on an oral contraceptive pill (65.6% vs. 37.5%).

“Based on these observations, we recommend that females being treated with spironolactone also be placed on an oral contraceptive pill,” says Nowsheen.

However, antibiotics may not play a key role in treating female adolescent acne. “Our data did not show much benefit from concomitant antibiotic treatment. Therefore, we recommend that physicians should refrain from prescribing antibiotics to help reduce emergence of bacterial resistance,” she adds.

FEW SIDE EFFECTS

Tolerability of spironolactone was good and comparatively better than in the adult population that was the subject of the previous study. In the pediatric cohort, 3 patients (3.8%) experienced side effects that resulted in treatment discontinuation. The side effects included rash, breast tenderness, diarrhea and headache.

“Side effects with spironolactone that have been reported in the literature include hyperkalemia, gastrointestinal disturbances and irregular menses,” says Nowsheen. “Considering that very few patients in our study experienced side effects and eventually had to stop treatment and because no patients developed symptoms suggestive of hyperkalemia, we do not recommend any routine laboratory monitoring for patients being treated with spironolactone for acne.”

Disclosures:

Dr. Nowsheen has no relevant financial interests to disclose.

References


Age influences choice of rosacea therapies

Most patients with rosacea are satisfied with the current oral and topical prescription therapies they are using to treat this skin condition, according to a recently published study by the National Rosacea Society (NRS). However, the data also reveal age-related trends in preferred therapies. According to survey results, patients 60 years and older are more likely to use older treatments instead of newer therapies, even if they are potentially more effective in targeting specific signs and symptoms.

Researchers surveyed 1,714 patients with rosacea. Of those patients, 54% of the 60-and-over population group report they are still using prescription therapies that were the first-ever developed and approved products for rosacea versus 41% of patients under 60. Additionally, survey results reveal 42% of patients 60 and over with rosacea continue to use their same treatment regimen versus 19% of patients under 60.

“These findings suggest that older patients should talk with their doctors about newer therapeutic options,” says Linda Stein Gold, MD, director of dermatology clinical research at the Henry Ford Health System. “Rosacea is now understood to include a variety of possible combinations of signs and symptoms, and there is currently a range of medical therapies that will address them individually,” she adds. “In addition, taking more than one medication as prescribed may have a synergistic effect to achieve more successful results.”
INDICATIONS AND USAGE
ZILXI (minocycline) topical foam, 15% is a tetracycline-class drug indicated for the treatment of inflammatory lesions of rosacea in adults.

Limitations of Use: This formulation of minocycline has not been evaluated in the treatment of infections. To reduce the development of drug-resistant bacteria as well as to maintain the effectiveness of other antibacterial drugs, ZILXI should be used only as indicated.

IMPORTANT SAFETY INFORMATION

Contraindications
Persons who have shown hypersensitivity to any of the tetracyclines or any other ingredient in ZILXI.

Warnings and Precautions
Flammability: The propellant in ZILXI is flammable. Instruct the patient to avoid fire, flame, and smoking during and immediately following application.

ZILXI is a topical foam. While systemic absorption of ZILXI is low, and serious adverse reactions were not seen in clinical studies, the following adverse reactions associated with oral minocycline should be considered:

IMPORTANT SAFETY INFORMATION, CONTINUED

• Teratogenic effects, inhibition of bone growth & permanent tooth discoloration: Use during the second and third trimesters of pregnancy, infancy and childhood up to the age of 8 years may cause permanent discoloration of the teeth (yellow-gray-brown) and reversible inhibition of bone growth.

• Clostridioides difficile associated diarrhea (CDAD): If CDAD occurs, discontinue ZILXI.

• Hepatotoxicity & metabolic effects: If renal impairment exists or if liver injury suspected, discontinue ZILXI.

• Central nervous system effects: Patients experiencing light-headedness, dizziness or vertigo should be cautioned about driving vehicles or operating heavy machinery.

• Intracranial hypertension: Clinical manifestations include headache, blurred vision, diplopia, and vision loss. Discontinue ZILXI immediately if symptoms occur.

• Autoimmune syndromes: Symptoms may be manifested by fever, rash, arthralgia, and malaise. Discontinue ZILXI immediately if symptoms occur.
The first time minocycline has been approved for rosacea

Zilxi is the first and only topical minocycline proven effective in adult patients with inflammatory lesions of rosacea

- Evaluated in 2 large, 12-week phase 3 trials (N=1522)
- Significantly reduced inflammatory lesion count by Week 12
- Demonstrated improvement in IGA treatment success by Week 12

Proven safe and well-tolerated on already-sensitive skin

- The most commonly reported adverse reaction was diarrhea (1%)
- Zilxi was well-tolerated throughout the treatment period

Delivered in a gentle, proprietary foam vehicle

- Leverages Molecule Stabilizing Technology (MST)™ for stable topical delivery
- Contains naturally moisturizing ingredients, is surfactant-free, and does not contain drying agents, such as ethyl alcohol

IMPORTANT SAFETY INFORMATION, CONTINUED

Photosensitivity: Patients should minimize or avoid exposure to natural or artificial sunlight while using ZILXI. Advise patients to discontinue treatment with ZILXI at the first evidence of sunburn.

Hypersensitivity reactions: Discontinue ZILXI immediately if symptoms of anaphylaxis, serious skin reactions, erythema multiforme, and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome occur.

Tissue hyperpigmentation: Discoloration of organs, including nails, bone, skin, eyes, thyroid, visceral tissue, oral cavity (teeth, mucosa, alveolar bone), sclerae and heart valves.

Superinfection: Overgrowth of non-susceptible organisms, including fungi if superinfection occurs, discontinue ZILXI and institute appropriate therapy.

Adverse Reactions
The most common adverse reaction reported during clinical trials of ZILXI was diarrhea.

IGA-Investigator’s Global Assessment.

*Co-primary endpoints at Week 12 were absolute change from baseline in inflammatory lesion count and IGA treatment success. IGA treatment success was defined as an IGA score of 0 or 1 (clear or almost clear) and at least a 2-grade improvement (decrease) from baseline. Patients were included if they had 15–75 facial lesions (papules and pustules), no more than 2 facial nodules, and an IGA score of moderate or severe (grade 3 or 4) (N=1522).†

†Zilxi 1.5% topical foam contains the following inactive ingredients: soybean oil, coconut oil, light mineral oil, cyclomethicone, cetostearyl alcohol, stearic acid, myristyl alcohol, hydrogenated castor oil, white wax (beeswax), stearyl alcohol, docosanol, and propellants (butane + isobutane + propane).†

REFERENCES: 1. ZILXI™ (minocycline) topical foam, 1.5% Prescribing Information. Bridgewater, N.J: Foamix Pharmaceuticals Inc; 2020.

Please see Brief Summary of Prescribing Information for ZILXI on the following pages.

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COM-ZIL-US-200041 09/2020
ZILXI™ (minocycline) topical foam, 1.5%
BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION.
PLEASE SEE FULL PRESCRIBING INFORMATION.

INDICATION
ZILXI is indicated for the treatment of inflammatory lesions of rosacea in adults.

Limitations of Use: This formulation of minocycline has not been evaluated in the treatment of infections. To reduce the development of drug-resistant bacteria as well as to maintain the effectiveness of other antibacterial drugs, ZILXI should be used only as indicated.

CONTRAINDICATIONS
This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines or any other ingredients within ZILXI.

WARNINGS AND PRECAUTIONS
• Flammability: The propellant in ZILXI is flammable. Instruct the patient to avoid fire, flame, and smoking during and immediately following application. Do not puncture or incinerate the containers. Do not expose containers to heat or flame at temperatures above 120°F (49°C).
• Teratogenic Effects: Minocycline, like other tetracycline-class drugs, may inhibit bone growth when administered orally during pregnancy. Based on animal data, when administered orally, tetracyclines cross the placenta, are found in fetal tissues, and can cause skeletal malformation and retardation of skeletal development on the developing fetus.
• Tooth Discoloration: The use of tetracycline class drugs orally during tooth development (second and third trimesters of pregnancy, infancy, and childhood up to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). This adverse reaction is more common during long-term oral use of the tetracycline but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported with oral tetracycline drugs. Use of tetracycline drugs is not recommended during tooth development.
• Inhibition of Bone Growth: All tetracyclines form a stable calcium complex in any bone-forming tissue. A decrease in fibula growth rate has been observed in premature human infants given oral tetracycline in doses of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the drug was discontinued. Results of animal studies indicate that oral tetracyclines cross the placenta, are found in fetal tissues, and can cause retardation of skeletal development on the developing fetus. Evidence of embryotoxicity has been noted in animals treated orally early in pregnancy.
• Clostridioides difficile Associated Diarrhea: Clostridioides difficile associated diarrhea (CDAD) has been reported with nearly all antibacterial agents, including oral minocycline, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile. C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin-producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. If CDAD is suspected or confirmed, antibiotic use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, and antibiotic treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.
• Hepatotoxicity: Post-marketing cases of serious liver injury, including irreversible drug-induced hepatitis and fulminant hepatic failure (sometimes fatal) have been reported with oral minocycline use.
• Metabolic Effects: The anti-anabolic action of the tetracyclines may cause an increase in blood urea nitrogen (BUN). In patients with significantly impaired function, higher serum levels of tetracycline-class drugs may lead to azotemia, hyperphosphatemia, and acidosis. If renal impairment exists, recommended oral or parenteral dosages may lead to excessive systemic accumulations of the drug and possible liver toxicity. Under such conditions, adjust the dose downward, and if therapy is prolonged, serum level determinations of the drug may be advisable.
• Central Nervous System Effects: Central nervous system side effects including light-headedness, dizziness or vertigo have been reported with oral minocycline therapy. Patients who experience these symptoms should be cautioned about driving vehicles or using hazardous machinery while on minocycline therapy. These symptoms may disappear during therapy and may disappear when the drug is discontinued.
• Intracranial Hypertension: Intracranial hypertension has been associated with the use of tetracycline-class drugs. Clinical manifestations of intracranial hypertension include headache, blurred vision, diplopia and vision loss; papilledema can be found on fundoscopy. Women of childbearing age who are overweight or have a history of IH are at a greater risk for developing intracranial hypertension. Patients should be questioned for visual disturbances prior to initiation of treatment with tetracyclines. Concomitant use of isoretinoin and tetracycline should be avoided because isoretinoin, a systemic retinoid, is also known to cause intracranial hypertension. Although intracranial hypertension typically resolves after discontinuation of treatment, the possibility for permanent visual loss exists. If visual disturbance occurs during treatment, prompt ophthalmologic evaluation is warranted. Because intracranial pressure can remain elevated for weeks after drug cessation, patients should be monitored until they stabilize.
• Autoimmune Syndromes: Tetracyclines have been associated with the development of autoimmune syndromes. The long-term use of oral minocycline has been associated with drug-induced lupus-like syndrome, autoimmune hepatitis and vasculitides. Sporadic cases of serum sickness have presented shortly after oral minocycline use. Symptoms may be manifested by fever, rash, arthritis, and malaise. In symptomatic patients, immediately discontinue the use of all tetracycline-class drugs, including ZILXI.
• Photosensitivity: Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking oral tetracyclines; this reaction has been reported less frequently with minocycline. Although ZILXI did not induce phototoxicity or photoallergic responses in human dermal safety studies, patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVAB treatment) while using minocycline. If patients need to be outdoors while using ZILXI, they should wear loose-fitting clothes that protect skin from sun exposure and discuss other sun protection measures with their physician. Advise patients to discontinue treatment with ZILXI at the first evidence of sunburn.
• Serious Skin/Hypersensitivity Reaction: Cases of anaphylaxis, serious skin reactions (e.g. Stevens Johnson syndrome, erythema multiforme, and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome have been reported postmarketing with oral minocycline use. DRESS syndrome consists of cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, and one or more of the following visceral complications such as: hepatitis, pneumonitis, nephritis, myocarditis, and pericarditis. Fever and lymphadenopathy may be present. In some cases, death has been reported with oral minocycline use. If this syndrome is recognized, discontinue ZILXI immediately.
• Tissue Hyperpigmentation: Oral tetracyclines are known to cause hyperpigmentation. Tetracycline therapy may induce hyperpigmentation in many organs, including nails, bone, skin, eyes, thyroid, visceral tissue, oral cavity (teeth, mucosa, alveolar bone), sclerae and heart valves. Skin and oral pigmentation has been reported to occur independently of time or amount of drug administration, whereas other tissue pigmentation has been reported to occur upon prolonged administration. Skin pigmentation includes diffuse pigmentation as well as pigmentation over sites of scars or injury.
• Development of Drug-Resistant Bacteria: ZILXI has not been evaluated in the treatment of infections. Bacterial resistance to the tetracyclines may develop in patients using ZILXI, therefore, the susceptibility of bacteria associated with infection should be considered in selecting antimicrobial therapy. Because of the potential for drug-resistant bacteria to develop during the use of ZILXI, it should be used only as indicated.
• Superinfection/Potential for Microbial Overgrowth: Use of ZILXI may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, discontinue ZILXI and institute appropriate therapy.

ADVERSE REACTIONS
• Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In three (two Phase 3 and one Phase 2) multicenter, randomized, double-blind, vehicle-controlled trials, adult subjects applied ZILXI or vehicle once daily for 12 weeks. A total of 1,087 subjects were treated with ZILXI and 591 with vehicle. The majority of subjects were White (97%) and female (70%). Approximately 67% were non-Hispanic/Latino. The mean age was 50.0 years and ages ranged from 18 to 86 years.
• The most common adverse reaction reported by ≥1% of subjects treated with ZILXI and more frequently than in subjects treated with vehicle was diarrhea (1% vs. 0%), respectively.

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• During the two Phase 3 trials, local tolerability evaluations were conducted at each study visit by assessment of erythema, telangiectasia, burning/stinging, flushing/blushing, dryness, itching, peeling and hyper-pigmentation. Subjects treated with ZILXI had improved local tolerability signs and symptoms at Week 12 when compared with corresponding baseline values. These occurred at a similar frequency and severity as subjects treated with the vehicle component of ZILXI. The local tolerance assessments in ZILXI patients (N = 1,008, of which 897 had local tolerability assessments at week 12) by incidence rate (%) and severity grade were as follows (mild, moderate, severe): erythema (36.2%, 18.3%, 0.7%), Telangiectasia (61.0%, 18.8%, 0%), burning/stinging (13.3%, 2.8%, 0%), flushing/blushing (39.0%, 9.6%, 0.9%), dryness (23.9%, 4.0%, 0.1%), itching (20.0%, 3.3%, 0%), skin peeling (16.1%, 1.9%, 0.1%), and hyperpigmentation (22.5%, 2.8%, 0%). Hyperpigmentation was most frequently assessed as characteristic of inflammatory and post-inflammatory changes associated with inflammatory lesions of rosacea. In a 40-week open-label extension safety study (for a total of up to 52 weeks of treatment) [NCT03276936], frequency and severity of local tolerability signs and symptoms at Week 52 were comparable to those reported at Week 12.

DRUG INTERACTIONS
• Anticoagulants: Because tetracyclines have been shown to decrease plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.
• Penicillin: Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracycline-class drugs in conjunction with penicillin.
• Drug/Laboratory Test Interactions: False elevations of urinary catecholamine levels may occur due to interference with the fluorescence test.

USE IN SPECIFIC POPULATIONS
• Pregnancy: Risk Summary: Available data with ZILXI use in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. Systemic absorption of ZILXI in humans is low following once daily topical application of ZILXI under maximal clinical use conditions. Because of low systemic exposure, it is not expected that maternal use of ZILXI will result in significant fetal exposure to the drug. Tetracycline-class drugs may cause permanent discoloration of teeth and reversible inhibition of bone growth when administered orally during pregnancy. Animal reproduction studies were not conducted with ZILXI. In animal reproduction studies, oral administration of minocycline administered to pregnant rats and rabbits during organogenesis induced skeletal malformations in fetuses at systemic exposures of 2,000 and 1,300 times, respectively, the maximum recommended human dose (MRHD based on AUC comparison) of ZILXI (see Data). The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.
• Data: Animal Data: Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can cause retardation of skeletal development of the developing fetus. Minocycline induced skeletal malformations (bent limb bones) in fetuses when orally administered to pregnant rats and rabbits during the period of organogenesis at doses of 30 mg/kg/day and 100 mg/kg/day, respectively, (2,000 and 1,300 times, respectively, the systemic exposure at the MRHD based on AUC comparison). Reduced mean fetal body weight was observed when minocycline was orally administered to pregnant rats during the period of organogenesis at a dose of 10 mg/kg/day (680 times the systemic exposure at the MRHD based on AUC comparison).
• Minocycline was assessed for effects on peri- and post-natal development of rats in a study that involved oral administration to pregnant rats during the period of organogenesis through lactation, at doses of 5, 10, or 50 mg/kg/day. In this study, body weight gain was significantly reduced in pregnant females that received 50 mg/kg/day (1,700 times the systemic exposure at the MRHD based on AUC comparison). No effects of treatment on the duration of the gestation period or the number of live pups born per litter were observed. Gross external anomalies observed in F1 pups (offspring of animals that received oral minocycline) included reduced body size, improperly rotated forelimbs, and reduced size of extremities. No effects were observed on the physical development, behavior, learning ability, or reproduction of F1 pups, and there was no effect on gross appearance of F2 pups (offspring of F1 animals).

• Lactation: Risk Summary: Tetracycline-class drugs, including minocycline, are present in breast milk following oral administration. It is not known whether minocycline is present in human milk after topical administration to the nursing mother. There are no data on the effects of minocycline on milk production. Because of the potential for serious adverse reactions, advise patients that breastfeeding is not recommended during treatment with ZILXI.

• Pediatric Use: The safety and effectiveness of ZILXI for the treatment of inflammatory lesions of rosacea have not been evaluated in pediatric patients.
• Geriatric Use: There were 278 subjects aged 65 or older in the clinical trials of ZILXI (16.6% of 1,678 subjects). No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

NONCLINICAL TOXICOLOGY
• Carcinogenesis, Mutagenesis, Impairment of Fertility: In a carcinogenicity study in which minocycline hydrochloride was orally administered to male and female rats once daily for up to 104 weeks at dosages up to 200 mg/kg/day, minocycline hydrochloride was associated in both sexes with follicular cell tumors of the thyroid gland, including increased incidences of adenomas, carcinomas and the combined incidence of adenomas and carcinomas in males, and adenomas and the combined incidence of adenomas and carcinomas in females. In a carcinogenicity study in which minocycline hydrochloride was orally administered to male and female mice once daily for up to 104 weeks at dosages up to 150 mg/kg/day, exposure to minocycline hydrochloride did not result in a significantly increased incidence of neoplasms in either males or females. Minocycline was not mutagenic in vitro in a bacterial reverse mutation assay (Ames test) or CHO/HGPRT mammalian cell assay in the presence or absence of metabolic activation. Minocycline was not clastogenic in vitro using human peripheral blood lymphocytes or in vivo in a mouse micronucleus test.
• Male and female reproductive performance in rats was unaffected by oral doses of minocycline of up to 300 mg/kg/day (27,500 times the systemic exposure at the MRHD based on AUC comparison). However, oral administration of 100 or 300 mg/kg/day of minocycline to male rats (10,000 or 27,500 times, respectively, the systemic exposure at the MRHD based on AUC comparison), adversely affected spermatogenesis. Effects observed at 300 mg/kg/day of oral minocycline included a reduced number of sperm cells per gram of epididymis, an apparent reduction in the percentage of sperm that were motile, and (at 100 and 300 mg/kg/day) increased numbers of morphologically abnormal sperm cells. Morphological abnormalities observed in sperm samples included absent heads, misshapen heads, and abnormal flagella.

• Handling: Allow the can to warm to room temperature before first use. Shake well before use.
• Warning: Flammable. Avoid fire, flame, or smoking during and immediately following application. Contents under pressure. Do not puncture or incinerate. Do not expose to heat or temperatures above 49°C (120°F).

For more information, including the FDA-approved Prescribing Information, go to www.ZILXI.com or call 1-844-375-3673.

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Typically, dermatologists diagnose rosacea through a physical examination, but this method is subject to high intra- and inter-observer variability when assessing patients. However, according to a study funded by the National Rosacea Society (NRS), researchers found that a computer diagnostic tool, Ros-NET, is able to accurately identify rosacea.

The study was conducted by a research team from Ohio State University’s (OSU) Department of Dermatology and the Wake Forest School of Medicine, and was led by Benjamin Kaffenberger, MD, associate professor of dermatology at OSU Wexner Medical Center.

“…we proposed a quantitative and reproducible computer-aided diagnosis system, Ros-NET, which integrates information from different image scales and resolutions in order to identify rosacea lesions,” write Binol H, Plotner A, et al.

Initially, investigators sought to construct an algorithm that was similar to one they had created previously for acne to help better identify rosacea. However, the team was able to utilize artificial intelligence (AI) to build a “deep learning” algorithm that is specifically tailored for identifying rosacea.

Ros-NET uses digital images shot in natural white light to locate areas on the face affected by rosacea. Also, the algorithm does not require assistance in locating areas that are possibly affected by rosacea. It utilizes natural facial features to define facial boundaries and lighting to recognize areas prone to rosacea, according to a press release from NRS.

Investigators collected over one million images of patients with rosacea from current databases in order to train the algorithm’s identification abilities.

During the study, clinical findings, images and demographics were gathered from 166 patients diagnosed with rosacea.

The study found that Ros-NET was able to accurately recognize rosacea in patients roughly 88-90% of the time.

“Using a leave-one-patient-out cross-validation scheme, the weighted average Dice coefficients, in percentages, across all patients (N = 41) with 256 × 256 image patches are 89.8 ± 2.6% and 87.8 ± 2.4% with Inception-ResNet-v2 and ResNet-101, respectively,” the study authors report.

In addition, the algorithm was not able to recognize all of the various symptoms and lesions associated with rosacea, including papules, pustules, nasal swelling, telangiectasia, erythema and facial flushing. The AI-powered diagnostic tool was not able to further detail the affected areas.

While the algorithm’s identification capabilities for rosacea are high, researchers see a need for further development of the technology through implementation of more of patient images in an effort to improve diagnostic accuracy and identification of various symptoms of the skin condition, according to an NRS press release.

“The findings from this study support that pre-trained networks trained via transfer learning can be beneficial in identifying rosacea lesions,” Binol H, Plotner A, et al write. “Our future work will involve expanding the work to a larger database of cases with varying degrees of disease characteristics.”

References:
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Review links GI disorders, rosacea

Immunity, inflammation, signaling and bacterial overgrowth could play roles.

MARY SCOVIAK | Managing Editor

The therapies targeting inflammatory gastrointestinal (GI) disorders may play a future role in addressing immune system dysregulation and the rosacea symptoms that arise from it, according to a recent systematic review published in Dermatology Therapy. The article, which reviewed literature based on the associations between rosacea, skin and gut disorders, and GI disorders suggests future studies should focus on specific mechanisms linking GI pathology with rosacea manifestations and the role of enteral drugs in mitigating cutaneous symptoms.

Current theories highlight the role of the cutaneous microbiome, specifically *Demodex folliculorum* and a few commensal bacteria, in the propagation of an inflammatory response and its associated inflammatory effects in rosacea's pathogenesis, wrote first author Hala Daou, MS IV, University of South Florida Morsani College of Medicine.

In their review of the literature in PubMed, Cochrane, and Embase from their inception to August 6, 2020 (154 of the 708 papers gathered from database searches received full text review), the authors considered articles on current theories implicating immunity dysregulation, aberrant neurovascular signaling, chronic inflammation and overgrowth of commensal skin organisms, as well as associations with additional GI pathologies, including small intestinal bacterial overgrowth (SIBO), irritable bowel syndrome (IBS), inflammatory bowel disease (IBD) and *Helicobacter pylori* infection.

Also of interest were results on the generation of reactive oxygen species (ROS) due to an altered innate immune response that, according to Daou, “appears to be a component of rosacea’s mechanism of disease. Studies demonstrated higher levels of ROS in patients with this condition.”

**STUDIES IN THE REVIEW DISCUSS:**

- **The cutaneous membrane:** Skin affected by rosacea has significantly more expression of cathelicidin than normal skin, which may result in aberrant downstream effects and may also represent a link between rosacea and IBD.

- **Demodex folliculorum** (*D. folliculorum*): A study notes an association between *D. folliculorum* and inflammatory markers, “suggesting a deleterious activation of the immune system.” The cytokines observed (including interleukin [IL]-8 and tumor necrosis factor alpha [TNFa]) promote angiogenesis, highlighting a potential cause of the long-standing, prominent telangiectasias often present in rosacea.

- **Bacillus oleronius**: This microorganism produces antigenic proteins that potentially play a role in papulopustular rosacea (PPR), erythematos telangiectatic rosacea (ETR) and ocular rosacea.

- **Staphylococcus epidermidis**: The altered microenvironment of rosacea-affected skin could potentiate exacerbation of symptoms due to a shift in microflora.

- **The gut microbiome:** One case study shows a significant association between rosacea and a variety of systemic disorders including allergies, respiratory disease, GI disorders, hypertension, urogenital disease, and female hormonal imbalance; while a later population-based cohort study of 50,000 Danish patients with rosacea shows the prevalence of celiac disease (CeD), Crohn's disease (CD), ulcerative colitis (UC), small intestinal bacterial overgrowth (SIBO), and irritable bowel syndrome (IBS) were all significantly higher among patients with rosacea compared to controls.

- **IBD**: Increased risk of rosacea in patients with UC and CD is almost threefold compared to patients without IBD. A shared autoimmune susceptibility may provide a link between rosacea and GI disorders.

- **H. pylori**: A theorized association describes *H. pylori* inflammation via cytotoxins and gastrin-induced flushing. There is speculation that systemic effects may be due to increased mucosal permeability to alimentary antigens, an autoimmune mechanism via the production of cross-reactive antibodies, or the impairment of vascular integrity.

- **SIBO**: Patients with rosacea are 13 times more likely to have SIBO than controls.

Current studies are investigatig erenumab, a human monoclonal antibody that antagonizes the calcitonin gene-related peptide receptor (CGRP), timolol, a nonselective b-adrenergic antagonist and rifaximin, a semisynthetic nonsystemic antibiotic that acts as an intraluminal agent. 

Pulsed dye laser treatment with oxymetazoline-tetracycline hydrochloride 1% cream for the treatment of telangiectasia is also being studied. “The results of these studies will be formative in the future rosacea treatment arsenal,” wrote Daou.

**Disclosures:**

The authors report no relevant disclosures.

**References:**


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AN MH life sciences® BRAND
Now that there are effective therapies available to combat each sign and symptom, it is possible to tailor treatment to the needs of each patient.”

Linda Stein Gold, MD, director of dermatology clinical research at the Henry Ford Health System, Detroit

Rosacea therapies

Survey results also show differences in treatment between older and younger rosacea patients stretched to various other therapies.

The NRS survey reports patients younger than age 60 are more than twice as likely to use topical ivermectin (Stromectol, Merck; Soolantra, Galderma) when compared with patients 60 and over (20.7% versus 9%), as well as times more likely to use topical oxymetazoline (Rho-fade, EPI Health) (6.9% versus 1.4%) Meanwhile, both age ranges regularly use a prescription formulation of azelaic acid foam (Finacea, Leo Pharma), with 15.1% of patients under 60 and 13% of those 60 and over, respectively. Respondents had the option of selecting multiple treatments. Results show 22% of surveyed patients use over-the-counter products.

Results also show topical metronidazole to be the most commonly used past treatment, with 50% reporting past usage. Meanwhile, 40% report past usage of prescription doxycycline tablets or extended release capsules, and 22% having used prescription azelaic acid foam.

Of patients who changed treatments, 28% attribute the switch to dissatisfaction with previous treatment results, while 23% say a medical professional prescribed a new treatment. Also, 9% report a change in treatment because their insurance no longer covers the product.

Data also reveal that 69% of respondents would consult their dermatologist about a different or new treatment option that they thought would possibly help their rosacea.

According to the NRS, rosacea can develop in a variety of ways and can be onset at any age. However, data from patient surveys show that the skin condition commonly presents itself after age 30, leading to increased prevalence and population impact in older age groups.

“Today’s approach to rosacea treatment is different than in the past, when there were few options in our tool kit to address the variable signs and symptoms that may be present in an individual case,” Stein Gold notes. “Now that there are effective therapies available to combat each sign and symptom, it is possible to tailor treatment to the needs of each patient.”

The NRS survey asked respondents to rate their satisfaction with their treatment results on a scale of 1 to 5, with 5 being the most satisfied. Patients report overall satisfaction with their results no matter what treatment option they were utilizing. Nearly all had weighted average satisfaction scores of 3.5 or higher and no respondents reported below a 3.

Approximately 56% of patients with rosacea report clear or almost clear skin on most days—30% with mild rosacea, 12% with moderate and 1% severe, respectively.

“It’s important that patients follow directions on exactly how and when to apply each medication and use it consistently. Rosacea can often be successfully kept at bay, especially if patients take the medication exactly as prescribed,” says Stein Gold. “Not only will a partnership between a patient and their doctor produce the best results, appropriate management may help slow progression of the disease as well as maintain remission.”

The survey also touched on the impact of the COVID-19 pandemic on rosacea treatment, with 56% of respondents reporting they consulted a dermatologist regarding their skin condition within the past year while 18% report seeing a physician within the past three years. Asked about teledermatology, 15% of those surveyed used the service and would use it again; 40% have not used it but are considering it.

SURVEY QUESTION: WHAT PRODUCT(S) ARE YOU CURRENTLY USING FOR YOUR ROSACEA?

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Under 60</th>
<th>60 and Older</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metronidazole Cream/Gel</td>
<td>40.5%</td>
<td>53.9%</td>
<td>51.2%</td>
</tr>
<tr>
<td>Ivermectin Cream 1%</td>
<td>20.7%</td>
<td>9.1%</td>
<td>11.5%</td>
</tr>
<tr>
<td>Azelaic Acid Foam 15%</td>
<td>15.1%</td>
<td>13.0%</td>
<td>13.4%</td>
</tr>
<tr>
<td>Oxymetazoline HCL Cream 1%</td>
<td>6.9%</td>
<td>1.4%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Doxycycline Oral Tablets (50mg or higher)</td>
<td>9.9%</td>
<td>12.7%</td>
<td>12.0%</td>
</tr>
<tr>
<td>Doxycycline, USP 40mg Delayed Release Capsules</td>
<td>5.6%</td>
<td>2.8%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Minocycline Oral Tablets</td>
<td>4.0%</td>
<td>3.2%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Brimonidine Topical Gel 0.33%</td>
<td>1.3%</td>
<td>1.5%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Other Prescription Treatment</td>
<td>22.4%</td>
<td>18.0%</td>
<td>19.0%</td>
</tr>
<tr>
<td>Over-the-Counter (OTC) product</td>
<td>26.3%</td>
<td>20.4%</td>
<td>21.7%</td>
</tr>
</tbody>
</table>

References:
Does molluscum keep him away from his friends?

When left untreated, symptoms last an average of 13 months and can last for as long as 4 years.¹⁻³

Many dermatologists believe that early treatment of molluscum may¹,²,⁴,⁵:

- Reduce disease progression
- Control the number of lesions and decrease the potential for scarring
- Avoid the spread to other areas of the body or to other people
- Prevent onset and exacerbation of comorbidities such as atopic dermatitis
- Reduce discomfort and itching
- Prevent social exclusion from school or extracurricular activities
- Alleviate anxiety in children and caregivers
- Improve quality of life for patients

A recent survey shows that only half of patients are satisfied with their atopic dermatitis (AD) treatment. Yet only around one-third regularly discuss quality of life with their healthcare providers.

Between December 2019 and April 2020, 408 adults answered an 80-question online survey sponsored by Health Union, a patient resource that supports healthcare communities including AtopicDermatitis.net.

“It’s telling that only 49% are satisfied with the care they’re receiving,” says Sara Hayes, executive director of community development at Health Union. “Often, satisfaction with your physician or healthcare team correlates strongly to how well-controlled you feel on your treatment plan.”

Among other key findings, only 36% of respondents report that their healthcare providers regularly discuss quality of life with them. “That’s a big thing for healthcare professionals to understand — they need to ask more about how this condition is impacting patients day-to-day,” she says.

Only 56% of respondents reported completely agreeing with their healthcare provider on the severity of their disease. While clinicians typically gauge severity through clinical measures such as body surface area, Hayes says, they should also factor in quality-of-life impact. “It’s a little disheartening for people to be told something is mild when they feel it’s consuming their lives,” Hayes says. “We’ve also heard stories of people who find it embarrassing when their skin starts to become weepy and oozes, and sometimes can bleed. These open wounds can cause social anxiety and invite infections.”

Elsewhere, the survey reflects high levels of topical corticosteroid (TCS) use and associated concerns. For example, 42% of patients report continuous TCS use for five years. While patients may not use TCS daily, Hayes explains, they may continually refill the prescription to use intermittently for each flare.

Meanwhile, more than half of respondents worry about topical steroid side effects, addiction and withdrawal. Experts estimate that approximately 12% of patients with AD who use topical steroids develop topical steroid addiction (TSA). Instead of having a psychological compulsion, patients must continually use TCS or their eczema flares. During topical steroid withdrawal (TSW), symptoms may worsen beyond pretreatment levels. This process often leads to red skin syndrome (RSS), in which painful redness develops in the application area and spreads elsewhere. Patients can become bedbound. Some patients describe this as the lowest point in their lives, she says.

Hayes finds it equally concerning that 31% of respondents have never heard of TSW. Not surprisingly, following physicians’ orders is a “huge topic” in the AD community, she says. While many patients plan to stop using TCS before their skin becomes somewhat addicted, she says, they don’t necessarily consider the future — they want relief now.

Patients tend to follow their physicians’ instructions, she says. “But when they don’t see results, they’ll go back to the doctor and perhaps get a higher potency steroid. That pattern repeats until they’re using very strong steroids.”

In the survey, 47% of patients required a higher-strength topical steroid, although less than two-thirds of this group ultimately achieved skin clearance.

Furthermore, only 15% of respondents are satisfied with TCS. “That’s an awfully low number. Many people consider atopic dermatitis ‘just eczema.’ They don’t fully understand how much it impacts patients’ quality of life.”

Some patients may skip topical steroid doses or avoid TCS entirely. “There’s a good portion of the community who have that fear of the potential side effects. So they use them only sparingly and absolutely when needed.”

On a positive note, 39% of respondents actively seek information about the latest AD treatments. Although many types of treatments are under development, says Ms. Hayes, patients find new biologics particularly exciting. “We see that 42% of respondents feel that they’ve done everything they can, and their condition is still not controlled. New research and potentially new drugs being approved in the future are exciting for them for patients who feel they’re out of options,” she adds.

References:

Disclaimers: Ms. Hayes is executive director of community development with Health Union.

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- Express Scripts National Preferred Formulary†
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- Prime Therapeutics
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Indicates no DMARD or biologic step-edit required

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INDICATIONS

Otezla® (apremilast) is indicated for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

Otezla is indicated for the treatment of adult patients with active psoriatic arthritis.

IMPORTANT SAFETY INFORMATION

Contraindications

- Otezla® (apremilast) is contraindicated in patients with a known hypersensitivity to apremilast or to any of the excipients in the formulation

Please see additional Important Safety Information and Brief Summary of Full Prescribing Information on the following pages.
## Important Safety Information (Cont’d)

### Warnings and Precautions

- **Diarrhea, Nausea, and Vomiting:** Cases of severe diarrhea, nausea, and vomiting have been reported with the use of Otezla. Most events occurred within the first few weeks of treatment. In some cases patients were hospitalized. Patients 65 years of age or older and patients taking medications that can lead to volume depletion or hypotension may be at a higher risk of complications from severe diarrhea, nausea, or vomiting. Monitor patients who are more susceptible to complications of diarrhea or vomiting; advise patients to contact their healthcare provider. Consider Otezla dose reduction or suspension if patients develop severe diarrhea, nausea, or vomiting.

- **Depression:** Treatment with Otezla is associated with an increase in depression. During clinical trials 1.3% (12/920) of patients reported depression, compared to 0.4% (2/506) on placebo. Suicidal behavior was observed in 0.1% (1/1308) of patients on Otezla, compared to 0.2% (1/506) on placebo. Carefully weigh the risks and benefits of treatment with Otezla for patients with a history of depression and/or suicidal thoughts/behavior, or in patients who develop such symptoms while on Otezla. Patients, caregivers, and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal thoughts or other mood changes, and they should contact their healthcare provider if such changes occur.

- **Weight Decrease:** Body weight loss of 5-10% occurred in 12% (96/784) of patients treated with Otezla and in 5% (19/382) of patients treated with placebo. Monitor body weight regularly; evaluate unexplained or clinically significant weight loss, and consider discontinuation of Otezla.

- **Drug Interactions:** Apremilast exposure was decreased when Otezla was co-administered with rifampin, a strong CYP450 enzyme inducer; loss of Otezla efficacy may occur. Concomitant use of Otezla with CYP450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin) is not recommended.

### Adverse Reactions

- Adverse reactions reported in ≥5% of patients were (Otezla®, placebo%): diarrhea (17, 6), nausea (17, 7), upper respiratory tract infection (9, 6), tension headache (8, 4), and headache (6, 4).
For adult patients with moderate to severe plaque psoriasis

**OTEZLA SIGNIFICANTLY IMPROVES SCALP RESPONSE**

STYLe primary endpoint: proportion of patients achieving an ScPGA response at week 16

43.3% with Otezla® (apremilast) 30 mg BID (n=201)  
13.7% with placebo (n=102)  
(P<0.0001)

*ScPGA response was defined as the proportion of patients achieving an ScPGA score of 0 (clear) or 1 (almost clear) with at least a 2-point reduction from baseline.

Results seen in an Otezla patient (scalp response)

- The most common adverse reactions (≥5%) from weeks 0 to 16 included diarrhea, nausea, headache, and vomiting
- The proportion of patients who discontinued treatment because of any adverse reaction was 6% for patients who received Otezla 30 mg twice daily and 3% for patients who received placebo
- Gastrointestinal adverse reactions that led to discontinuation of treatment were diarrhea (3% vs 0%), nausea (1.5% vs 1%), and vomiting (1.5% vs 0%) in the Otezla group, compared to placebo

Visit OtezlaPro.com for additional information

**IMPORTANT SAFETY INFORMATION (cont’d)**

Use in Specific Populations

- Pregnancy: Otezla has not been studied in pregnant women. Advise pregnant women of the potential risk of fetal loss. Consider pregnancy planning and prevention for females of reproductive potential. There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Otezla during pregnancy. Information about the registry can be obtained by calling 1-877-311-8972 or visiting https://mothertobaby.org/ongoing-study/otezla/
- Lactation: There are no data on the presence of apremilast or its metabolites in human milk, the effects of apremilast on the breastfed infant, or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for Otezla and any potential adverse effects on the breastfed child from Otezla or from the underlying maternal condition
- Renal Impairment: Otezla dosage should be reduced in patients with severe renal impairment (creatinine clearance less than 30 mL/min); for details, see Dosage and Administration, Section 2, in the Full Prescribing Information

Of the reported adverse drug reactions none were serious.

**NOTE:**

WARNINGS AND PRECAUTIONS

Diarrhea, Nausea, and Vomiting

There have been rare reports of severe diarrhea, nausea, and vomiting associated with the use of OTEZLA. Most events occurred within the first few weeks of treatment. In some cases patients were hospitalized. Patients 65 years or older and patients taking medications that can lead to volume depletion or hypotension may be at a higher risk of complications from severe diarrhea, nausea, or vomiting. Monitor patients who are more susceptible to complications of diarrhea or vomiting. Patients who reduced dosage or discontinued OTEZLA generally improved quickly. Consider OTEZLA dose reduction or suspension if patients develop severe diarrhea, nausea, or vomiting.

**Depression**

Treatment with OTEZLA is associated with an increase in adverse reactions of depression. Before using OTEZLA in patients with a history of depression and/or suicidal thoughts or behavior prescribers should carefully weigh the risks and benefits of treatment with OTEZLA in such patients. Patients, their caregivers, and their families should be monitored closely for the appearance of suicidal ideation and/or behavior and should be counseled to recognize the early features of depression or suicidality and to report them to their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment with OTEZLA if such events occur.

**Psoriasis**

During the 0 to 16 week placebo-controlled period of the 3 controlled clinical trials, Treatment Protocol 1, Treatment Protocol 2, and Treatment Protocol 3, the percentage of patients who experienced at least one adverse reaction of depression or depressive mood or depression was reported in 8.0% (3/38) of subjects treated with OTEZLA compared to none in placebo-treated subjects (0/38). Depression was reported as serious in 1.3% (2/156) of subjects exposed to OTEZLA compared to none in placebo-treated subjects (0/156). Instances of suicidal ideation and behavior have been observed in 0.4% (6/1560) of patients while receiving OTEZLA compared to none in placebo-treated subjects (0/1560). Suicidal ideation and behavior have been observed in 0.2% (3/1441) of subjects exposed to OTEZLA compared to none in placebo-treated subjects (0/1441). Suicidal ideation and behavior have been observed in 0.1% (1/1308) of subjects treated with OTEZLA discontinuum treatment due to depression or depressive mood compared to none in placebo-treated subjects (0/1308).

**Drug Interactions**

Apremilast pharmacokinetics were characterized in subjects with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment as defined by a creatinine clearance of 60 -89, 30-59, and less than 30 mL per minute, respectively, by the Cockcroft & Gault equation.

**Contraindications**

OTEZLA is contraindicated in patients with a known hypersensitivity to apremilast or to any of the excipients in the formulation [see Adverse Reactions (6.1)].

**Usage in Specific Populations**

**Pediatric Use**

The safety and effectiveness of OTEZLA in pediatric patients less than 18 years of age have not been established.

**Geriatric Use**

Of the 1425 patients who enrolled in Studies PsA-1, PsA-2, and PsA-3 a total of 146 psoriatic arthritis patients were 65 years of age and older. No overall differences were observed in the safety profile of elderly patients 65 years of age and younger adult patients < 65 years of age in the clinical studies.

**Renal Impairment**

Apremilast pharmacokinetics were characterized in subjects with mild, moderate, and severe renal impairment as defined by a creatinine clearance of 60-89, 30-50, and less than 30 ml per minute, respectively, by the Cockcroft-Gault equation. While no dose adjustment is needed in patients with mild or moderate renal impairment, the dose of OTEZLA should be reduced to 30 mg once daily in patients with severe renal impairment [see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)].

**Hepatic Impairment**

Apremilast pharmacokinetics were characterized in subjects with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment. No dose adjustment is necessary in these patients.

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- COREY MASS, MD
JAKs may predict psoriasis risk

Genetic polymorphisms may increase psoriasis susceptibility.

JOHN JESITUS | Staff Correspondent

Variants in Janus kinase (JAK)1 rs310241 and JAK3 rs3008 may increase susceptibility to psoriasis, according to a recent study.1 JAKs have attracted significant interest in dermatology, says corresponding author Aya M. AlOrbani, MD, lecturer in dermatology at Cairo University Hospital, Cairo, Egypt. “But the focus has mainly been on JAKs as a therapeutic target.”

Clinical studies have shown that JAK inhibition improves diseases such as psoriasis, vitiligo and alopecia areata. “But not many studies have assessed how genetic changes or polymorphisms in the JAK genes could affect psoriasis,” she says.

To further explore the genetic architecture of psoriasis, investigators in the Kasr Al-Ainy Psoriasis Unit (KAPU), Cairo University Hospital, compared blood samples from 150 Egyptian patients with psoriasis and samples from 120 age- and sex-matched healthy volunteers.

Using the polymerase chain reaction (PCR)-restriction fragment length polymorphism technique, investigators screened samples for nucleotide polymorphisms in JAK1 rs310241 and JAK3 rs3008. They chose these variants partly because the JAK1 rs310241 polymorphism has been associated with other immune-mediated illnesses such as Crohn’s disease and Behçet’s disease.

Investigators noted that the GG (homozygous) genotypes of JAK1 rs310241 and JAK3 rs3008 conferred approximately 7.7-fold and 3.3-fold increased risk for psoriasis, respectively.1 P values were 0.000 and 0.003, respectively; 95% confidence intervals (CIs) were 2.8-21.5 and 1.5-6.9, respectively.

“Polymorphisms are like genetic markers,” says AlOrbani. “The discovery that these polymorphisms exist may help us predict which patients are at high risk of developing psoriasis in the future.” Further down the road, she adds, this knowledge may help physicians tailor treatments to patients’ individual clinical situations. “The next step might be to study the effect of these polymorphisms on response to treatments.”

JAKs are basically secondary messengers that mediate biological signaling, she says. “Inflammatory cytokines bind to receptors, and JAK molecules are recruited.” JAK activation triggers a cascade of further signaling events involving phosphorylation of selected receptor chain tyrosines, binding of signal transcription and activator of transcription (STAT) proteins and phosphorylation of these STATs.

For both JAK polymorphisms studied, frequency of the G allele was significantly higher in patients with psoriasis versus controls and significantly increased the risk of psoriasis. “Patients who had the G allele in the JAK1 gene had twice the risk of developing psoriasis, and those with the JAK3 allele had a 1.7-fold increased risk,” says AlOrbani.

Regarding gender, researchers noted no difference in polymorphisms in patients with psoriasis was gender-dependent. However, the Korean study detected both protective and susceptibility loci in JAK2.

“Ethnicities differ,” she says. “The JAK polymorphisms might make a difference in studies repeated in different populations.”

Disclosures: Aya M. AlOrbani, MD reports no relevant financial interests.

References:
1 Sayed KS, El-Komy MM, Elshababi H, et al. JAK1 rs310241 and JAK3 rs3008 genotypes may increase susceptibility to psoriasis: a case control study.[published online before print September 2, 2020]. Skin Pharmacol Physiol. 2020;33:207-212.
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Safety profiles differentiate conventional therapies

Concerns linger over potential to cause long-term cumulative organ toxicity.

JOHN JESITUS | Staff Correspondent

Highlighting the relationship between long-term safety and drug survival, a recent review1 may help address physician reluctance in prescribing conventional systemic psoriasis therapies.

Even with increasingly early use of biologics, first author Deepak M. W. Balak, MD, PhD, says most psoriasis guidelines still recommend older oral systemic therapies as first-line treatment. He is a consultant dermatologist at LangeLand Hospital in Zoetermeer, the Netherlands.

“Safety is a clinically important issue in older treatments given their broader mechanisms of action compared to the targeted biologics,” he adds. “Our review aims to help clinicians better understand their safety profile in order to use them more appropriately.”

When used appropriately, says Balak, conventional systemic agents can provide a significant proportion of patients with excellent disease control and safety. However, he adds that clinicians who lack extensive clinical experience with these agents may not use them optimally, leading to negative treatment outcomes or unnecessary adverse effects.

“In general, most clinicians are quite reluctant to use these oral treatments because they have the potential to cause long-term cumulative organ toxicity,” he says. “For instance, methotrexate is linked to hepatotoxicity, and cyclosporine can cause kidney injury. By knowing the safety profiles and adequately selecting and monitoring your patients, you can avoid these toxicities and maintain safe, effective long-term treatment.”

Balak and his fellow researchers searched EMBASE and PubMed through November 2018 for publications discussing drug safety over at least six months and identified 157 relevant publications. Investigators found that acitretin could be associated with skeletal toxicity (hyperostosis) and hepatotoxicity, although evidence for both is mixed. Additional safety issues include hyperlipidemia and potential teratogenicity up to three years after drug discontinuation.

Long-term studies of apremilast are rare. However, a handful of trials with up to three years’ follow-up suggests that the most common adverse events (AEs) include nausea, diarrhea, upper respiratory tract infection, nasopharyngitis and headache. Depression and suicidal ideation have been reported, although these risks remain unclear. Fortunately, continued exposure appears not to increase incidence of these common AEs, and apremilast requires no standard blood monitoring.

Long-term cyclosporine therapy may not be advisable due to nephropathy (which is reversible at doses less than 5 mg/kg/day), hypertension and risks of end-organ toxicity. Cyclosporine also increases risks of nonmelanoma skin cancer and of photocarcinogenic potential during long-term treatment, particularly in patients who have undergone high cumulative psoralen and UVA (PUVA) doses.

Methotrexate requires expert supervision, says the authors, because it can have severe, wide-ranging AEs on multiple organs and organ systems including the gastrointestinal tract, kidneys, liver and lungs. Accordingly, patients with diabetes mellitus, obesity or excessive alcohol consumption should preferentially avoid methotrexate, as these patients are at-risk to develop methotrexate-related hepatotoxicity. Long-term fumaric acid ester (FAE) therapy is associated most commonly with gastrointestinal complaints, flushing and abnormal white blood cell counts, in particular low-grade lymphocytopenia.

The findings of their literature study largely reinforced the authors’ clinical approach to using these agents, says Balak.

Most drugs showed widely variable drug survival rates, owing to differences in safety, efficacy, patient satisfaction and other factors. Inter-study variability was a concern. For example, a registry study showed one-, three- and five-year survival rates of 63%, 30% and 15%, respectively, for methotrexate. In another study, 60% of patients discontinued methotrexate at an average of 4.2 months. Improving the standardization of safety outcome reporting would enable more accurate comparisons between studies, says Balak.

“Choosing a systemic therapy for psoriasis could pose challenges in clinical practice. We hope that our review will support well-balanced decision-making for long-term psoriasis management and help clinicians to better understand for which patient you would prescribe which oral treatment.”

Disclosures:

Dr. Balak is a consultant and/or speaker for AbbVie, Almirall, Celgene, Eli Lilly, Janssen Pharmaceuticals, Leo Pharma, Novartis International and Sanofi-Aventis. He also has received research grants from Leo.

References:

Apremilast

Research & Education Foundation, Irvine, California, and lead author of the study. He adds, “Switching to alternative psoriasis medications is a common practice in the long-term management of patients with moderate-to-severe disease. The increase in healthcare costs after changing treatment plans is likely due to more frequent physician appointments as newly administered medications can result in more side effects.”

Wu and fellow researchers recently conducted a study comparing the healthcare costs associated with treatment switching among biologic-naive patients with psoriasis, initiating apremilast or biologic therapy with up to 12 months pre/post-index continuous enrollment using data from the Optum Clinformatics™ Data Mart (CDM).

Initially, the researchers identified 62,578 patients as having a new treatment episode with apremilast from January 2014 and September 2016. Of that total, 2,746 patients were eligible for analysis after applying the inclusion/exclusion criteria.

After propensity score matching, Wu and his fellow authors assessed switch rates (new therapy post-index) and days to switch. Results reveal that apremilast initiators have significantly lower 12-month cumulative switch rates and days to switch. They defined switch rate as the cumulative proportion of patients who switched to a new treatment (apremilast or biologic) at 3, 6, 9, 12, 15, 18, 21 and 24 months after initiation of the index treatment. The majority of biologic therapies included adalimumab, followed by ustekinumab, etanercept, secukinumab (Cosentyx, Novartis Pharmaceuticals) and ixekizumab (Taltz, Lilly).

Although proven to be very effective in addressing psoriasis symptoms, these systemic treatments used alone or in combination with topical treatments can be expensive. “Psoriasis is a life-long disease and many times, whatever medications patients are going to be put on, they will have to eventually switch to another therapy to manage their disease, which can incur significant costs to this patient population who are reliant on these medications,” said Jashin J. Wu, MD, director, Dermatology Research & Education Foundation. Wu adds that it may not be optimal for those patients with severe psoriatic disease, defined as affecting 10% or more of the body surface.

When contemplating appropriate therapy, I use comorbidities as a compass to guide my treatment selection,” Wu says. “For patients with severe psoriatic disease, I would go with a biologic therapy because they are more effective in clearing the psoriasis. Patients with psoriatic arthritis, which occurs in about one-third of patients with psoriasis, probably should receive biologic therapy. In those with both psoriasis and psoriatic arthritis, I prefer to prescribe IL-17 inhibitors or TNF inhibitors.”

Apremilast is FDA-approved for both psoriasis and psoriatic arthritis, and the lower overall healthcare costs of apremilast compared to the biologics may make it more cost-effective for the patient, an outcome also seen in other similar studies. According to Wu, cost-comparative studies can help direct clinicians and their patients towards more cost-effective treatment regimens. 4

Disclosures: Dr. Wu has been an investigator, consultant, or speaker for AbbVie, Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Dermira, Dr. Reddy’s Laboratories, Lilly, Gilead Sciences, Janssen, Leo Pharma, Novartis, Regeneron, Sanofi, Shionogi, Sun Pharmaceutical, UCB, Vektor BioPharma, North America LLC.

Reference:
Melanoma immunotherapy focuses on personalization

Faster response rate reviews, new therapies help tailor treatment.

GINA MAURO | Editorial Director, OncLive

With an estimated five-year survival rate of 50% and an ongoing issue of resistance, the next steps with immunotherapy in melanoma will focus on stratifying patients, personalizing therapy and refining localized regimens, says Georgina Long, AO, BSc, PhD, MBBS, FRACP, FAHMS, co-medical director of Melanoma Institute Australia (MIA), and chair of Melanoma Medical Oncology and Translational Research at MIA and Royal North Shore Hospital, The University of Sydney.

“We have benchmarks for our standard treatments. We can explore more new, novel therapies, look at [patients’] pathologic complete response rates within six weeks and then make decisions on whether they need further development. This is the future,” according to Long’s presentation at the recent virtual 17th International Congress of the Society for Melanoma Research."  

A review the current overall survival (OS) rates yielded with this approach summarizes where the field is now, says Long. Five-year OS rates with BRAF inhibitors combined with methyl ethyl ketone (MEK) inhibitors, programmed cell death protein (PD)-1 inhibitors alone, and PD-1 plus cytotoxic T-lymphocyte-associated protein (CTLA)-4 inhibitors are 34%, 44% and 52%, respectively, leaving room for improvement, she says.

Triplet regimens with immunotherapy were a natural next step in an attempt to further improve outcomes, although results have been modest, according to Long. For example, in the phase 2 KEYNOTE-022 trial, pembrolizumab (Keytruda, Merck) was evaluated in combination with dabrafenib (Tafinlar, Novartis) and trametinib (Mekinist, Novartis) in patients with treatment-naïve BRAF V600E/K-mutant, advanced melanoma compared with dabrafenib/trametinib plus placebo. At the 24 month follow-up, the triplet led to a 47% reduction in the risk of disease progression or death compared with the doublet therapy (HR, 0.53; 95% CI, 0.34-0.83).

Similarly, in the IMspire150 trial, frontline atezolizumab (Tecentriq, Genentech) and cobimetinib (Cotellic, Genentech) in patients with untreated BRAF V600E/K-mutant melanoma, was randomized 1:1:1 to encorafenib/binimetinib until disease progression, followed by nivolumab/ipilimumab (arm A); nivolumab/ipilimumab until disease progression, followed by encorafenib/binimetinib (arm B); or nivolumab/ipilimumab for 8 weeks, followed by nivolumab/ipilimumab until disease progression, followed by encorafenib/binimetinib (arm C).

Results showed that the triplet led to a 22% reduction in the risk of disease progression or death versus vemurafenib/cobimetinib plus placebo (HR, 0.78; 95% CI, 0.63-0.97; P = .025). Most recently, an updated analysis of part 3 of the phase 3 COMBI-i trial showed that spartalizumab plus dabrafenib/trametinib in patients with untreated BRAF V600E-mutant metastatic melanoma did not meet its primary end point of investigator-assessed progression-free survival (PFS). However, although overall survival (OS) was not formally tested, a hazard ratio of 0.785 was observed in favor of the spartalizumab plus dabrafenib and trametinib combination.

“In summary, for these triplet therapies, the [results with] immune and targeted therapy together [were modest],” says Long. “There is a clinically minor added benefit, however with significant toxicity.”

Perhaps the “sandwich approach” would be optimal, she suggests. This strategy was used in the phase 2 Sequential COMB Immuno and Targeted Therapy (SECOMBIT) study and was presented during the 2020 European Society for Medical Oncology (ESMO) Virtual Congress. Patients with untreated metastatic BRAF V600–mutant melanoma were randomized 1:1 to encorafenib/binimetinib until disease progression, followed by nivolumab/ipilimumab (arm A); nivolumab/ipilimumab until disease progression, followed by encorafenib/binimetinib (arm B); or encorafenib/binimetinib for 8 weeks, followed by nivolumab/ipilimumab until disease progression, followed by encorafenib/binimetinib (arm C).

Results showed that the median progression-free survival (PFS) was 15.8 months, 7.2 months, and 11.4 months in arms A, B and C, respectively. While these data differed, the two-year (PFS) rates were similar at 35%, 38% and 39%, respectively.

More data are needed from this trial before applying any of these approaches to clinical practice, Long concludes.

Regarding checkpoint inhibitors, nivolumab, pembrolizumab and ipilimumab are all available for use in the adjuvant setting, along with the...
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- 15% CR (complete response)¹
- 31% PR (partial response)¹

ORR: 63 out of 137 patients (95% CI, 37%-55%)¹,²

- 79% of responders (50 out of 63 patients) reached a DOR of ≥6 months¹,²,³
- 54% of responders (34 out of 63 patients) reached a DOR of ≥12 months¹,²,³

*Median duration of follow-up was 11.1 months for combined CSCC in Study 1540. See additional study design details below.

In an additional cohort in Study 1540, 56 mCSCC patients received LIBTAYO at a dose of 350 mg intravenously every 3 weeks for up to 54 weeks. With a median duration of follow-up of 8.0 months, the confirmed ORR was 41% (95% CI: 28, 55), and 65% of responders had a DOR ≥6 months.¹

Median DOR was not reached (range: 2.1–11.1+ months)²

The recommended dosage of LIBTAYO is 350 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity.²

Important Safety Information

Warnings and Precautions

Severe and Fatal Immune-Mediated Adverse Reactions

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue and usually occur during treatment; however, they can also occur after discontinuation. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously. Early identification and management are essential to ensuring safe use of PD-1–blocking antibodies. Monitor for symptoms and signs of immune-mediated adverse reactions. Evaluate clinical chemistry, including liver tests and thyroid function tests, at baseline and periodically during treatment. Institute medical management promptly to include specialist consultation as appropriate.

In general, withhold LIBTAYO for Grade 3 or 4 and certain Grade 2 immune-mediated adverse reactions. Permanently discontinue LIBTAYO for Grade 4 and certain Grade 3 immune-mediated adverse reactions. For Grade 3 or 4 and certain Grade 2 immune-mediated adverse reactions, administer corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) or other appropriate therapy until improvement to Grade 1 or less followed by a corticosteroid taper over 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reaction is not controlled with corticosteroids. Institute hormone replacement therapy for endocrinopathies as warranted.

Immune-mediated pneumonitis: Immune-mediated pneumonitis occurred in 2.4% of 534 patients receiving LIBTAYO, including Grade 5 (0.2%), Grade 3 (0.7%), and Grade 2 (1.3%). Pneumonitis led to permanent discontinuation of LIBTAYO in 1.3% of patients. Systemic corticosteroids were required in all patients with pneumonitis, including 85% who received prednisone ≥40 mg/day or equivalent. Pneumonitis resolved in 62% of patients. Withhold LIBTAYO for Grade 2, and permanently discontinue for Grade 3 or 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper.

Immune-mediated colitis: Immune-mediated colitis occurred in 0.9% of 534 patients receiving LIBTAYO, including Grade 3 (0.4%) and Grade 2 (0.5%). Colitis led to permanent discontinuation of LIBTAYO in 0.2% of patients. Systemic corticosteroids were required in all patients with colitis, including 60% who received prednisone ≥40 mg/day or equivalent. Colitis resolved in 80% of patients. Withhold LIBTAYO for Grade 2 or 3, and permanently discontinue for Grade 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper.

Immune-mediated hepatitis: Immune-mediated hepatitis occurred in 2.1% of 534 patients receiving LIBTAYO, including Grade 5 (0.2%), Grade 4 (0.2%), and Grade 3 (1.7%). Hepatitis led to permanent discontinuation of LIBTAYO in 0.9% of patients. Systemic corticosteroids were required in all patients with hepatitis, including 91% who received prednisone ≥40 mg/day or equivalent. Hepatitis resolved in 64% of patients. Withhold LIBTAYO if AST or ALT increases to more than 3 and up to 10 times the upper limit of normal (ULN) or if total bilirubin increases up to 3 times the ULN. Permanently discontinue LIBTAYO if AST or ALT increases to more than 10 times the ULN or total bilirubin increases to more than 3 times the ULN. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper.

Immune-mediated endocrinopathies: Withhold LIBTAYO if clinically necessary for Grade 2, 3, or 4. Adrenal insufficiency: Adrenal insufficiency occurred in 0.4% of 534 patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.2%). Hypophysitis: Hypophysitis, which can result in hypopituitarism, occurred in 0.2% of 534 patients receiving LIBTAYO, which consisted of 1 patient with Grade 3 hypophysitis. Hyperthyroidism: Hyperthyroidism occurred in 6% of 534 patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (5.6%), no patients discontinued hormone replacement therapy.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information on the following pages.
**Important Safety Information (continued)**

### Warnings and Precautions (continued)

#### Severe and Fatal Immune-Mediated Adverse Reactions

**Immune-mediated endocrinopathies (continued):**

- **Hyperthyroidism:** Hyperthyroidism occurred in 1.5% of 534 patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.4%). Hyperthyroidism resolved in 38% of patients with systemic corticosteroids.
- **Type 1 diabetes mellitus:** Type 1 diabetes mellitus, which can present with diabetic ketoacidosis, occurred in 0.7% of 534 patients, including Grade 4 (0.4%) and Grade 3 (0.4%). Type 1 diabetes mellitus led to permanent discontinuation of LIBTAYO in 0.2% of patients.

**Immune-mediated nephritis with renal dysfunction:** Immune-mediated nephritis occurred in 0.6% of 534 patients receiving LIBTAYO, including Grade 3 (0.4%) and Grade 2 (0.2%). Nephritis led to permanent discontinuation of LIBTAYO in 0.2% of patients. Systemic corticosteroids were required in all patients with nephritis, including 67% who received prednisone ≥40 mg/day or equivalent. Nephritis resolved in all patients. Withhold LIBTAYO for Grade 3, and permanently discontinue for Grade 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper.

Other immune-mediated adverse reactions: The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% in 534 patients who received LIBTAYO, including those with disease progression:

- **Neurological:** Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome, nerve palsies, and autoimmune neuropathy
- **Cardiovascular:** Myocarditis, pericarditis, and vasculitides

### Use in specific populations

- **Lactation:** Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for at least 4 months after the last dose of LIBTAYO.

### References

3. Additional information is available at REGN2810Regeneron.com.

To learn more about LIBTAYO, speak with your sales representative or visit LIBTAYOhcp.com.
CONTRAINDICATIONS

Immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, all possible immune-mediated reactions. Important immune-mediated adverse reactions listed under Warnings and Precautions may not be inclusive of None.

Identify and manage immune-mediated pneumonitis, dermatologic reactions, including 89% who received prednisone after re-initiation of LIBTAYO.

Approximately 22% of patients had recurrence of dermatologic reactions, including 89% who received prednisone after re-initiation of LIBTAYO.

40 mg per day or equivalent. Pneumonitis resolved in 62% of patients.

Grade 3 (0.7%) and Grade 2 (1.3%) [see Adverse Reactions (6.1)]. Colitis led to permanent discontinuation of LIBTAYO in 0.2% of patients. Systemic corticosteroids were required in all patients with colitis, including 60% who received prednisone ≥ 40 mg per day or equivalent. Colitis resolved in 83% of patients.

Hypothyroidism occurred in 1.5% of 534 patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.7%). Hypothyroidism led to permanent discontinuation of LIBTAYO in 0.9% of patients. Systemic corticosteroids were required in all patients with hypothyroidism, including 91% who received prednisone ≥ 40 mg per day or equivalent. Hypothyroidism resolved in 64% of patients.

The safety population characteristics were: median age of 72 years (38 to 96 years), 83% male, 96% white, and 77% non-Hispanic white. The most common Grade 3-4 adverse reactions (≥ 10% of patients) and Table 2 summarizes Grade 3—4 adverse reactions resulting in permanent discontinuation were pneumonitis, cough, pneumonia, encephalitis, aseptic meningitis, hepatitis, arthropathy, muscle weakness, neck pain, soft tissue necrosis, complex regional pain syndrome, lethargy, paresthesia, rash, maculopapular, pruritus, and confusional state. Serious adverse reactions occurred in 35% of patients. Serious adverse reactions that occurred in at least 2% of patients were pneumonitis, colitis, rash, and dermatitis.

Table 1 summarizes the adverse reactions that occurred in ≥ 10% of patients and Table 2 describes Grade 3 or 4 laboratory abnormalities worsening from baseline in ≥ 1% of patients receiving LIBTAYO.

Table 1: Adverse Reactions in ≥ 10% of Patients with Advanced CSCC Receiving LIBTAYO in Study 1423 and Study 1540

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>LIBTAYO N=219</th>
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<tr>
<td></td>
<td>All Grades</td>
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<td></td>
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<tr>
<td>General and Administration Site</td>
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<tr>
<td>Fatigue</td>
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<td>Pruritus</td>
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<tr>
<td>Constipation</td>
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</tr>
<tr>
<td>Vomiting</td>
<td>10</td>
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<tr>
<td>Musculoskeletal and Connective Tissue</td>
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<tr>
<td>Arthritis</td>
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<tr>
<td>Respiratory</td>
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(continued)
Table 1: Adverse Reactions in ≥10% of Patients with Advanced CSCC Receiving LIBTAYO in Study 1423 and Study 1548 (continued)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
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<td></td>
<td>All Grades</td>
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<td>Anemia</td>
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<td>Hypothyroidism</td>
<td>10</td>
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<tr>
<td>Metabolism and Nutrition</td>
<td>10</td>
</tr>
</tbody>
</table>

Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.4.03.

- a. Fatigue is a composite term that includes fatigue and asthenia
- b. Rash is a composite term that includes rash, rash maculopapular, erythema, dermatitis, dermatitis bullous, rash generalized, pemphigoid, rash erythematous, rash macular, rash pruritic, drug eruption, psoriasis, and skin reaction
- c. Pruritus is a composite term that includes pruritus and pruritus allergic
- d. Diarrhea is a composite term that includes diarrhea and colitis
- e. Musculoskeletal pain is a composite term that includes back pain, pain in extremity, myalgia, musculoskeletal pain, and neck pain
- f. Cough is a composite term that includes cough and upper airway cough syndrome

Table 2: Grade 3 or 4 Laboratory Abnormalities Worsening from Baseline in ≥1% of Patients with Advanced CSCC Receiving LIBTAYO in Study 1423 and Study 1548

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>2</td>
</tr>
<tr>
<td>Increased INR</td>
<td>2</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>9</td>
</tr>
<tr>
<td>Anemia</td>
<td>5</td>
</tr>
<tr>
<td>Electrolytes</td>
<td></td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>5</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>4</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>2</td>
</tr>
</tbody>
</table>

Toxicity graded per NCI CTCAE v.4.03.

- a. Percentages are based on the number of patients with at least 1 post-baseline value available for that parameter.
- b. Pain, including neck pain
- c. Rash generalized, pemphigoid, rash erythematous, rash macular, rash pruritic, drug eruption, psoriasis, and skin reaction
- d. Cough is a composite term that includes cough and upper airway cough syndrome
- e. Pruritus is a composite term that includes pruritus and pruritus allergic
- f. Diarrhea is a composite term that includes diarrhea and colitis
- g. Rash is a composite term that includes rash, rash maculopapular, erythema, dermatitis, dermatitis bullous, rash generalized, pemphigoid, rash erythematous, rash macular, rash pruritic, drug eruption, psoriasis, and skin reaction

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, LIBTAYO can cause fetal harm when administered to a pregnant woman (see Clinical Pharmacology (12.1)). There are no available data on the use of LIBTAYO in pregnant women. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death (see Data). Human IgG4 immunoglobulins (IgG4) are known to cross the placenta; therefore, LIBTAYO has the potential to be transmitted from the mother to the developing fetus. Advise women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Animal reproduction studies have not been conducted with LIBTAYO to evaluate its effect on reproduction and fetal development. A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. In murine models of pregnancy, blockade of PD-L1 signaling has been shown to disrupt tolerance to the fetus and to result in an increase in fetal loss; therefore, potential risks of administering LIBTAYO during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-1/PD-L1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice.

Based on its mechanism of action, fetal exposure to cemiplimab-rwlc may increase the risk of developing immune-mediated disorders or altering the normal immune response.

8.2 Lactation

Risk Summary

There is no information regarding the presence of cemiplimab-rwlc in human milk, or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for at least 4 months after the last dose of LIBTAYO.

8.3 Females and Males of Reproductive Potential

Contraception

LIBTAYO can cause fetal harm when administered to a pregnant woman (see Use in Specific Populations (8.1)).

- Females: Advise females of reproductive potential to use effective contraception during treatment with LIBTAYO and for at least 4 months after the last dose.

8.4 Pediatric Use

The safety and effectiveness of LIBTAYO have not been established in pediatric patients.

8.5 Geriatric Use

The safety and effectiveness of LIBTAYO have not been established in older patients.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, coadministered medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to cemiplimab-rwlc in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Anti-drug antibodies (ADA) were tested in 467 patients who received LIBTAYO. The incidence of cemiplimab-rwlc treatment-emergent ADAs was 1.1% using an electrochemiluminescent (ECL) bridging immunoassay; 0.2% were persistent ADA responses. In the patients who developed anti-cemiplimab-rwlc antibodies, there was no evidence of an altered pharmacokinetic profile of cemiplimab-rwlc.

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LIB 20.07.07 07/20
The big question is, should we be treating now with this adjuvant therapy, or should we treat later when we definitely have recurrence?”

Georgina Long, AO, BSc, PhD, MBBS, FRACPP, FAHMS, co-medical director of Melanoma Institute Australia (MIA), and chair of Melanoma Medical Oncology and Translational Research at MIA and Royal North Shore Hospital, The University of Sydney.

Reduction in the risks of disease progression or death using atezolizumab in combination with vemurafenib and cobimetinib in patients with unresectable advanced BRAF V600 mutation-positive melanoma versus vemurafenib/ cobimetinib plus placebo.

Combination of dabrafenib and trametinib.

“The big question is, should we be treating now with this adjuvant therapy, or should we treat later when we definitely have recurrence?” Long asks.

Some clues may come from the phase 3 CheckMate-238 trial, in which 906 patients who were undergoing complete resection of stage IIIB, IIIC, or IV melanoma were randomized to receive either nivolumab at 3 mg/kg every two weeks or ipilimumab at 10 mg/kg every three weeks for four doses and then every 12 weeks.

The 12-month rate of recurrence-free survival (RFS) was 70.5% (95% CI, 66.1-74.5) with nivolumab and 60.8% (95% CI, 56.0-65.2) with ipilimumab (HR, 0.65; 95% CI, 0.51-0.83; \( P < .001 \)).

Looking at the secondary end point, the four-year OS rate was 77.9% and 76.0% with nivolumab and ipilimumab, respectively (HR, 0.87; 95% CI, 0.66-1.14; \( P = .315 \)).

“We still need 100 or so events to analyze this properly, but it suggests that perhaps we can treat [patients] later,” Long adds.

Combination adjuvant immunotherapy with nivolumab and ipilimumab also showed an improvement in relapse-free survival versus nivolumab alone or a double-matching placebo group (HR, 0.23; 95% CI 0.13-0.14) in patients with resected stage IV melanoma in the double-blind, placebo-controlled phase 2 German IMMUNED study.

The combination of nivolumab and ipilimumab was evaluated again in the phase 3 CheckMate-915 trial—this time, in patients with resected stage IIIB/CD, or IV cutaneous or mucosal melanoma. Patients were randomized to receive nivolumab at 480 mg every four weeks or nivolumab at 240 mg every two weeks plus ipilimumab at 1 mg/kg every six weeks. Topline results showed that the combination compared with nivolumab alone did not meet its primary end point of relapse-free survival (RFS).

“Why [was this not a positive study]?” Long asks. “We don’t know yet, but could it be a dosing issue of ipilimumab, or could it be a protocol issue? If you develop toxicity on the nivolumab/ipilimumab arm, you couldn’t continue on nivolumab alone [on this trial], so maybe these patients received much less immunotherapy than needed due to toxicity. We do not do that in practice.”

Resistance to checkpoint inhibitors is an active area of investigation, especially as Long notes that 50% of patients progress on immunotherapy within six months.

Findings from the phase 2, single-arm LEAP-004 trial presented at ESMO show that the combination of lenvatinib and pembrolizumab elicited a confirmed objective response rate (ORR) by blinded independent central review of 21.4% in patients with advanced melanoma that has progressed on a PD-1/PD-L1 inhibitor.

Studies on response and resistance to immunotherapy in melanoma also explore the collection of tumor and tumor fragments/dissociates, blood, and feces and skin, Long explains. She looks to the neoadjuvant setting, where six weeks of preoperative therapy could be “the perfect model,” with pathologic complete response rate as a key measure.

Disclosures:
There are no relevant disclosures.

References:
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Quick TAKES

Recently FDA-approved for cutaneous BPDCN treatment, tagraxofusp yields high response but is associated with significant toxicities.

Venetoclax is being investigated in a phase 1 trial as an option for patients with BPDCN deemed unfit for tagraxofusp.

Transient neutropenia at week 8 of treatment was the only side effect, according to recent paper.¹

**“For patients deemed unfit for tagraxofusp, BCL-2 inhibition is a promising alternative and is currently being investigated in a phase I trial.”**

Matthew Schwede, MD, Hematology/Oncology Fellow at Stanford University School of Medicine, San Francisco, California.

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**Venetoclax may have role in cutaneous BPDCN**

**LISETTE HILTON | Staff Correspondent**

The B-cell lymphoma-(BCL)-2 inhibitor venetoclax may have a role in rapidly treating predominantly cutaneous blastic plasmacytoid dendritic cell neoplasm (BPDCN) with minimal systemic toxicity, according to a recently-published letter to the editor.¹

Clinicians might treat BPDCN with multi-agent chemotherapy, and while some patients experience remission on these regimens, remission is likely transient. Many believe BPDCN is incurable without allogeneic hematopoietic cell transplant, notes Matthew Schwede, MD, a Hematology/Oncology Fellow at Stanford University School of Medicine, San Francisco, California and his fellow investigators. The U.S. Food and Drug Administration (FDA) recently approved the cluster of differentiation (CD)123 directed cytotoxic tagraxofusp for BPDCN treatment, based on trials that yielded a 72% complete response and 90% overall response in newly-diagnosed patients. BPDCN arises from precursors of plasmacytoid dendritic cells, with immunohistochemical staining generally positive for CD4, CD56, CD123, and T-cell leukemia-(TCL)-1.²

“Tagraxofusp is associated with significant toxicities, including a potentially fatal capillary leak syndrome,” write the authors.

Venetoclax could be another treatment option, as recent in vitro studies have shown BPDCN depends on the BCL-2 protein to prevent apoptosis. In vivo research on BPDCN suggests animals treated with oral venetoclax have improved survival. Recent reports describe using venetoclax alone or in combination to treat newly diagnosed and relapsed/refractory BPDCN, write Schwede et al.³

Authors of a recently-published research brief² used primary tumor cell functional profiling to predict BCL-2 antagonist sensitivity as a common feature of BPDCN. They found in vivo clinical activity of venetoclax in patient-derived xenografts and in two patients with relapsed chemotherapy-refractory disease.

Schwede and his fellow authors add to the literature with a case of an 88-year-old man, presenting to his dermatologist with a 10-month history of what they described as progressive, nonulcerated, violaceous cutaneous plaques. The nonpruritic plaques appeared at first on his right lower leg, later on his left leg, chest, scalp and back. According to his dermatologist, the patient said topical steroids did not help.

Punch biopsies of the plaque showed dense, nodular and sheet-like, monomorphic infiltrate extending into the subcutis. Immunohistochemical studies revealed the cells were positive for CD4, CD56, CD123, TCL-1, and BCL-2, which is consistent with BPDCN.

“For our initial exam, the patient had indurated, well demarcated and violaceous plaques over the bilateral legs, chest, and back, with overlying scale on the plaques of the lower legs. The right lower extremity had tense edema. He was otherwise asymptomatic and strongly preferred to avoid hospitalization and potential treatment-related toxicities,” the authors write. After discussing all therapeutic options, they proceeded with venetoclax 400 mg daily.

The patient’s plaques markedly improved after four weeks. His right lower extremity plaque had minimal residual macular hyperpigmentation and no associated edema after eight weeks on venetoclax. The other lesions resolved completely, the authors add.

The only adverse effect was transient neutropenia at week 8 of treatment. “For patients deemed unfit for tagraxofusp, BCL-2 inhibition is a promising alternative and is currently being investigated in a phase I trial (NCT03485547),” write Schwede et al.⁴

Disclosures:
Two of the study’s authors have research, consulting or advisory roles with Gilead, Jazz Pharmaceuticals, Abbvie, Agios, BMS, Genentech and Pfizer.

References:
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"These technologies hold promise for procedures that are less invasive, have less downtime and are safer. It’s interesting none involves lasers."

Mathew Avram, MD, director of Lasers, Cosmetics, and Dermatologic Surgery,
Massachusetts General Hospital, Boston, Massachusetts.

Emerging therapies

Annual Virtual Meeting October 9-11.
Innovations like these could address some major current challenges, from improving the appearance of rhytids and skin laxity to clearing benign pigmented lesions, treating cellulite, and increasing the safety of dermal filler injections, says Avram, director of Lasers, Cosmetics, and Dermatologic Surgery at the Massachusetts General Hospital, Boston, Massachusetts.

“None of the emerging advances involves lasers,” Avram says. His presentation provides an overview of the novel modalities that are coming to market and/or seeking approval by the U.S. Food and Drug Administration (FDA).

SKIN SMOOTHING AND LIFTING
A proprietary micro-coring skin removal device (Cytrellis Biosystems), represents an entirely new category of technology in dermatologic surgery, according to Avram. Invented by dermatologists and plastic surgeons at Massachusetts General Hospital, it is a non-energy-based system for smoothing wrinkles and tightening skin. This device is currently undergoing FDA review for marketing clearance.

Applied to the skin on the cheeks, the device removes minute cores of skin (<500 μm in diameter) that account for about 8% of the skin in the area being treated. The procedure is performed with injected anesthesia with lidocaine with epinephrine. According to Avram, it is not painful and has just a few days’ downtime.

Avram says clinical results show improvement in wrinkles and skin laxity 90 days after the third treatment, although patients may experience redness and swelling. He adds that 75% of patients didn’t have to take time off of work, and the treatment is well tolerated, with the average pain reported as a 3.6 on a 0-to-10 scale. This is not a replacement for a facelift. But the results from the premarketing study show significant improvement in facial wrinkles and skin laxity that exceeds the benefits achievable with nonablative and fractional ablative devices,” he says.

PIGMENTED LESIONS
A novel dermal cooling system (CryoAesthetic, R2 Technologies) already has FDA clearance for treating benign pigmented lesions of the skin. Now, it’s being developed further to treat lentigines, seborrheic keratosis and other benign types of hyperpigmentation.

Avram says the device allows for more precise and controlled lesion freezing compared with conventional cryotherapy. There are other considerations when weighing it against laser treatments.“Although the treatment may not be quite as effective as a laser procedure, it is better tolerated and appears to result in fewer side effects and less downtime,” he says.

CELLULITE SOLUTION
Already cleared by the FDA for tattoo removal, a device that uses proprietary acoustic shockwaves (Rapid Acoustic Pulse, Soliton) is being developed as a completely noninvasive approach for treating cellulite.

Avram explains that the shockwaves shear the fibrotic septa that contribute to the appearance of cellulite dimpling by pulling the upper layers of skin down towards the superficial muscular aponeurotic system. Clinical trials show the procedure is well-tolerated without any anesthesia and takes about 20 to 30 minutes, which means it could be done in the office. In addition, there were no unexpected or serious adverse events and no downtime.

In the pivotal clinical trial, which included 67 subjects, the average procedural pain score rating was 2.4 out of 10. Among 62 patients included in the efficacy analysis, 85% were judged as treatment responders after a single session. Average percentage improvement in Cellulite Severity Score was 32.5% (range 6.7% to 85.7%), and 92% of patients agreed or strongly agreed that their cellulite appeared improved.

SAFETY INNOVATION
The design of a new “smart” needle (SInject, Blossom Innovations) aims to improve the safety of dermal filler injections. The device, also developed by a team at Massachusetts General Hospital, emits both audio and visual (light) alerts to surgeons as real-time feedback if the needle tip is positioned within a blood vessel.

“Accidental intra-arterial injection is the most feared complication of filler procedures because it can lead to tissue necrosis, ulceration, and even blindness if the filler is injected into the retinal artery,” says Avram. “Thankfully intra-arterial injection is an infrequent complication, but it is a significant concern considering its potentially devastating consequences and the millions of filler procedures performed each year.”

The sensing technology is in the needle itself; 27- and 28-gauge needles will be available first, other sizes will be added later. It is used in the same manner as conventional needles.

“This device is still undergoing investigation, but it holds valuable potential for preventing one of the most serious complications of a common dermatologic surgery procedure,” he adds.

Disclosure:
Mathew M. Avram, MD, JD, is on the medical advisory board to Soliton and the scientific advisory board to Cytrellis.
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Pandemic lessons

Slowing down allows time for reflection, retooling

JOHN JESITUS | Staff Correspondent

In the downtime created by the COVID-19 pandemic, some dermatologists are turning their attention to their own health and that of their specialty.

“Crises present many opportunities,” says Adam Friedman, MD. “You just have to look for them and jump on them.” He is professor and interim chair of dermatology, George Washington University (GW) School of Medicine and Health Sciences, Washington, D.C.

Amid travel bans and shelter-in-place orders in mid-March, many meetings including the American Academy of Dermatology (AAD) shut down, without contingency plans (AAD did launch its event as the AAD Virtual Annual Meeting Experience June 12-14, 2020). “I saw an opportunity there to leverage the virtual education we had been doing at GW to provide programming much more broadly.”

When the pandemic scotched large gatherings, he says, virtual education via live-streaming or recording became much cheaper and easier than assembling speakers and attendees for in-person events. Friedman mobilized resources so that on March 23, his department, in collaboration with MedStar Washington Hospital Center and Howard University, could present a free 7.5-hour virtual conference that drew 900 real-time attendees. A subsequent online acne symposium attracted 700 attendees.

By now, says Friedman, people are somewhat tired of virtual education and yearn for live conferences. However, in his view, online education still provides unprecedented flexibility. “You need to offer it in several ways, including live and archived, and in unique formats to engage the audience.”

Additionally, GW has opened all its resident didactic opportunities to virtual attendees. “From a national standpoint, in addition to people who rotate with us in the clinic, we have five to six virtual rotators every month.” For each rotator, the program includes a monthly 30-minute meeting with Friedman and his associate program director.

Joseph Zahn, MD. “It’s more work,” says Friedman, “but it’s worth it.”

On a broader scale, he says, the pandemic has nudged the needle regarding disparities in dermatology. “Our workforce does not mirror what the population looks like,” he says. When even photo atlases used for training lack diversity, results can include poor care for patients of color, he adds.

To foster inclusivity, Friedman has partnered with Solome Rose, master of public policy (MPP), an expert in diversity, inclusion and equity consultant, to institute a quarterly health-equity program that Friedman hopes one day to introduce nationwide. He credits COVID-19 for loosening industry purse strings and red tape to get the program started. “If this wasn’t the middle of the pandemic, where health disparities were so evident—and the anger, disappointment and hurt weren’t so palpable—I don’t know if we would’ve gotten this (instituting a quarterly health-equity program) funded at the level it needs to be funded.”

Adam Friedman, MD, professor and interim chair of dermatology, George Washington University (GW) School of Medicine and Health Sciences

Joseph Zahn, MD, “It’s more work,” says Friedman, “but it’s worth it.”

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The pandemic also allows time for reassessment. Joel Schlessinger, MD, says that instead of having daily hours from 7:30 AM until 5 PM, his practice now runs from 9 AM to 4:30 PM. “Slowing down allowed me to see the benefits of working a little less than I had prior to the pandemic,” says Schlessinger, an Omaha, Nebraska-based board-certified dermatologist and cosmetic surgeon and CEO of LovelySkin. “That may have affected our numbers, but it has made for a much happier life in general.”

Slowing down has allowed Schlessinger to work out daily rather than three times weekly. “The pandemic has been a terrible point in so many people’s lives including our own,” he adds. “But there are some positives.”

Wendy E. Roberts, MD, has learned that pre-pandemic, she wasted significant time chatting with sales reps and others who visited announced. “I have a hard time saying no when somebody wants to come in and see me,” says Roberts, a dermatologist and dermatopathologist in solo private practice in Rancho Mirage, California. “Now you do not get into this office unless your name is on a schedule.”

Another change, Roberts used to welcome late patients. “I can’t do that anymore. COVID has given me permission to be a little bit tougher and not have to apologize for it. I can’t run behind because there are people literally sitting out in their cars waiting to come in.”

Now, Roberts has more time for thoughtful pursuits such as writing articles and answering emails. “I’ve been more productive because my time in my office has been streamlined and structured.” And her patients have noticed. She estimates that 90% of them have complimented her on the more efficient office experience.

Disclosures: Drs. Friedman, Schlessinger and Roberts report no relevant financial interests.
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R. Rox Anderson, MD

DR. ANDERSON, recognized for his research, has advanced the basic knowledge of human skin photobiology, drug photosensitization mechanisms, tissue optics, and laser-tissue interactions. He conceived and developed many of the non-scarring laser treatments now widely used in medical care. These include treatments for birthmarks, microvascular and pigmented lesions, tattoos and permanent hair removal.

Notably, Dr. Anderson co-invented the fractional laser treatment, which is useful for improving burn scars, and recently invented and developed new devices for wound grafting without scarring.

Additionally, he has contributed to treatments for vocal cords, kidney stones, glaucoma, photodynamic therapy for skin cancer and acne, optical diagnostics and selective fat removal by tissue cooling.

“I’m thrilled to be honored in this way. I think of these awards as a chance, not so much for old guys like me to strut around, but to really motivate young people,” says Dr. Anderson in an interview you can find online at DermatologyTimes.com. “I’ve always just tried to help people and what a thrill to have an award like this as a consequence of basically just doing my job.”

He adds, “I really think this is an award to many people. It’s got my name on it, but really it’s an award that says we were successful in actually making a difference in dermatology, which is the bottom line.”

Dr. Anderson’s current research includes diagnostic tissue imaging and spectroscopy, photodynamic therapy, mechanisms of selective laser-tissue interactions, adipose tissue biology and novel therapies for skin disorders.

To date, he has been awarded more than 80 national and international patents and has co-authored over 250 scientific books and papers. Most recently, he received the William Silen Lifetime Achievement in Mentoring Award from Harvard Medical School and Harvard School of Dental Medicine and is being inducted into the National Academy of Inventors.

When asked about what the future of dermatology looks like, Dr. Anderson says the possibilities are endless.

“The future of the dermatology industry is going to go wherever it wants to go, wherever it needs to go. I think there are some predictable influencers. Now, we are in the midst of a pandemic where a lot of us are providing teledermatology and telemedicine. That’s not just a temporary shift,” says Dr. Anderson.

He adds that the dermatology industry will see more personalized virtual medical contact, including technology to aid in virtual skin checks and having ancillary exam tools be part of a virtual visit. Also, Dr. Anderson sees a rise in the world of lasers including further development of drug delivery through lasers.

“I guess, pun intended, one of the barriers in dermatology is stratum corneum, and the ability to get large molecules into the skin quickly and painlessly at known concentrations without a needle. I think that’s in our hands as well and that’s going to change things,” he says.
Wilma F. Bergfeld, MD, FAAD, FACP

DR. BERGFELD has a passion for dermatology, for teaching others about dermatology and for her patients, whom she prioritizes at her practice. In 1992, she was the first woman elected as president of the American Academy of Dermatologists (AAD), where she focused her efforts on environmental dermatology and communication with the public and members. “I’ve been in practice for over 55 years now and to be recognized at this time is wonderful,” says Dr. Bergfeld. “I’ve given my heart and soul to dermatology and teaching, and I’ve been very active nationally and internationally. So to be recognized at this time, at this part of my career, I’m delighted and humbled.” Since 1977, she has been a member and the chair (since 1990) of the Cosmetic Ingredient Review Expert Panel, which determines the safety of cosmetic ingredients. She holds an honorary membership in the AAD, Women’s Dermatologic Society, Cleveland Dermatological Society, Ohio Dermatological Association, Pacific Dermatologic Association, Canadian Dermatology Association and the Italian Society of Dermatology.

Dr. Bergfeld is the author of more than 700 publications, including 4 books, 83 book chapters, and 228 posters. She has served on many journal editorial boards and has been a reviewer in both of her professional fields of clinical dermatology and dermatopathology. She is the recipient of the Women’s Dermatologic Society Rose Hirschler Award honoring an outstanding physician who has contributed to medicine and dermatology while enhancing the role of women in the dermatology field. In 2000, she was the first recipient of the Wilma Bergfeld, MD Visionary & Leadership Award, also given by the Women’s Dermatologic Society. Dr. Bergfeld has also received countless accolades and has been cited in Best Doctors in America, Top Doctors, Top Pathologist, Best Award, also given by the Women’s Dermatologic Society. Since 1977, she has been a member and the chair (since 1990) of the Cosmetic Ingredient Review Expert Panel, which determines the safety of cosmetic ingredients. She holds an honorary membership in the AAD, Women’s Dermatologic Society, Cleveland Dermatological Society, Ohio Dermatological Association, Pacific Dermatologic Association, Canadian Dermatology Association and the Italian Society of Dermatology. Additionally, Dr. Bergfeld has been elected to serve on the board of directors of the American Academy of Dermatology and the International League of Dermatological Societies, where she has also served as secretary-general.

“I was actually very surprised when I learned my receiving this honor. I really didn’t expect expect it. I’m not sure who nominated me, but I’d like to thank him or her. I’d also like to thank my colleagues on the board of directors for selecting me as a finalist,” says Dr. Bolognia. She is the senior editor of the comprehensive textbook Dermatology, now in its fourth edition, and Dermatology Essentials, now in its second edition. These textbooks have been translated into eight languages.

Dr. Bolognia has delivered more than 60 named lectures. Her previous awards include the Gold Medal from the AAD, the Legacy Award from the Women’s Dermatologic Society, the Lifetime Career Educator Award from the Dermatology Foundation and the Lifetime Achievement Award from the Medical Dermatology Society. “I think this award reflects recognition by my peers of my decades of work trying to enhance the knowledge of my fellow dermatologists via the comprehensive textbook Dermatology, and the handbook Dermatology Essentials. . . I think the award also recognizes the hundreds of lectures I’ve given over the years. So, I want to give a big thanks to everyone involved,” she says.

J.L. Bolognia, MD

DR. BOLOGNIA is professor of dermatology at Yale School of Medicine in New Haven, Conn. Her key areas of interest include caring for patients who have nevi (moles), atypical nevi and skin cancer, including melanoma. She has served as president of the Medical Dermatology Society, the Women’s Dermatologic Society and the AAD. In addition, she has served as vice-president of the Society for Investigative Dermatology, the American Board of Dermatology and the International Society of Dermatology. Additionally, Dr. Bolognia has been elected to serve on the board of directors of the American Academy of Dermatology and the International League of Dermatological Societies, where she has also served as secretary-general.

“I practice [dermatology] because I enjoy it. And I do it mainly because I feel I can make a difference for my patients, educate and mentor the next generation of dermatologists, and contribute to our specialty,” says Dr. Lim. Some of Dr. Lim’s work includes more than 500 articles, edited nine textbooks, and served on the editorial boards of several journals. He is a recognized world authority on photodermatology.

Henry W. Lim, MD

DR. LIM is the former chair of the Department of Dermatology at Henry Ford Hospital and senior vice president of Academic Affairs at Henry Ford Health System in Detroit, Michigan. He received his doctor of medicine degree (cum laude) from SUNY Downstate Health Sciences University in Brooklyn, New York, and completed his dermatology residency at New York University School of Medicine in New York. He has previously served as president of the American Academy of Dermatology, American Board of Dermatology, American Dermatological Association, American Society for Photobiology, International Union of Photobiology and National Council on Skin Cancer Prevention. He is a board member of the International League of Dermatological Societies.

“I practice [dermatology] because I enjoy it. And I do it mainly because I feel I can make a difference for my patients, educate and mentor the next generation of dermatologists, and contribute to our specialty,” says Dr. Lim. Some of Dr. Lim’s work includes more than 500 articles, edited nine textbooks, and served on the editorial boards of several journals. He is a recognized world authority on photodermatology.

“... I think the award recognizes the hundreds of lectures I’ve given over the years. So, I want to give a big thanks to everyone involved,” she says.

Jouni Uitto, MD, PhD

I share this award with my international team of young scientists and, specifically, the students, postdoctoral fellows, residents and junior faculty that are the future of dermatology and cutaneous research.”

Dermatology Times.com DECEMBER 2020
**2020 Giants of Dermatology™**

He has been the recipient of the Fred W. Whitehouse Distinguished Career Award of the Henry Ford Medical Group, the European Academy of Dermatology and Venereology International Scientific Achievement Award, the International League of Dermatological Societies Certificate of Appreciation for International Leadership, the Finsen Medal from the International Union of Photobiology and the Alumni Achievement Award for Distinguished Service to American Medicine from the College of Medicine, SUNY Downstate.

Dr. Lim predicts the future of dermatology will be “extremely bright.”

“We know significantly more about the pathophysiology of the diseases which translates to better treatment, so I’m very optimistic that this field will continue to move forward scientifically and clinically. Most importantly, we will be able to help our patients even better than what we can do now,” Dr. Lim says.

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**Alan Menter, MD**

**DR. MENTER** has a long-held interest in psoriasis and psoriatic disease research that has spanned everything from ultraviolet phototherapy and new biologic therapy to the mapping of genetic patterns to predict whether a person is at risk of developing psoriasis pharmacogenomics. "I arrived here from England in 1975, so I've been here now for 45 years," says Dr. Menter. "I've created an international psoriasis council that I work with around the world and I do a lot of talks and studies and research, so I've gotten to know a lot of people, but I was truly honestly, very surprised that I was given this award and I'm very honored to receive it."

In 2004, Menter helped found the International Psoriasis Council to raise international awareness of psoriasis as a serious autoimmune disease that can significantly impact quality of life. In 1992, he was appointed chairman of the Division of Dermatology at Baylor University Medical Center in Dallas, Texas, and still holds that position. In 2007, he was appointed director of the Baylor Research Center and in 2010, program director of the Dermatology Residency Program at Baylor University Medical Center.

His resume lists some 426 articles, six books and 21 book chapters, and he serves as a member of the editorial board for several medical journals, including the Journal of Clinical Dermatology and Clinical and Experimental Dermatology.

Dr. Menter has been listed in Best Doctors in America since 1994 and in Who's Who in Medicine and Healthcare since 1996.

In 2013, he received the Lifetime Achievement Award from the National Psoriasis Foundation. In March 2015, he received the Dermatology Foundation annual Clark W. Finnerud Award at the AAD 73rd Annual Meeting in San Francisco, Calif.

Looking toward the future, Dr. Menter says the COVID-19 virus has played a significant role in shaping the outlook for dermatology. He cites the increased usage of teledermatology as a factor in the industry’s future. He adds, “I do believe teledermatology will continue to play a role, which it did not play previously.”

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**Jounei Uttø, MD, PhD**

**DR. UITTO** has been internationally recognized for his research on connective tissue biology and molecular genetics in relation to cutaneous diseases.

His has published more than 723 original articles in peer-reviewed journals, 349 textbook chapters and review articles and 1,043 abstracts in presentations at national and international meetings.

Additionally, Dr. Uttø serves as section editor of the Journal of Investigative Dermatology and associate editor of the American Journal of Pathology and sits on the editorial boards of numerous peer-reviewed journals.

In addition to being recognized as a 2020 Giant of Dermatology, Dr. Uttø has been the recipient of numerous national and international awards, including honorary doctorate degrees from the University of Eastern Finland, Kuopio, the University of Oulu and the University of Turku, all in Finland, as well as the University of Buenos Aires in Argentina. In addition, he has received honorary professorships from China Medical University, Shenyang; Fourth Military Medical University, Xi’an; and Hebei United University, Tangshan, all in China.

Dr. Uttø believes mentorship is the key to success, and since 1980, he has served as a mentor to over 140 graduate students, postdoctoral fellows and junior faculty, many of whom are now leading scientists as well as chairs in their respective fields.

“"This Giants of Dermatology award recognizes my career, not only as an academic dermatologist, but also my role as a physician, scientist and educator over the past four decades,” says Dr. Uttø. "I share this award with my international team of young scientists who have worked very hard over the years towards enhancing our understanding of the molecular basis of the heritable connective tissue and skin diseases with therapeutic implications. And I specifically want to share this award with over 140 graduate students, postdoctoral fellows, residents and junior faculty that are the future of dermatology and cutaneous research."
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**Position Highlights:**
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- Research interests not required

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- State College is more than just a quintessential college town. It is vibrant with exciting nightlife, great shopping, many options for arts & culture, and a diverse array of restaurants.
- State College Area School District ranks in the top 100 school districts in the State of Pennsylvania.
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FOR MORE INFORMATION PLEASE CONTACT:
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